CLINICAL PHARMACOKINETICS PHARMACY HANDBOOK

SECOND EDITION

PHARMACY PRACTICE & DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA

CLINICAL PHARMACOKINETICS

PHARMACY HANDBOOK

2019

PREPARED BY:

Clinical Pharmacy Working Committee

(Clinical Pharmacokinetics Subspecialty)

Pharmacy Practice & Development Division

Ministry of Health Malaysia

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FOREWORD

Clinical Pharmacy Service is an essential component of patient care which plays a role in managing medicines safely, effectively and efficiently central to the delivery of high quality care that is focused on the patient and gives value for money. In the 1980's, Therapeutic Drug Monitoring (TDM) service which is also known as Clinical Pharmacokinetics Service was introduced in Malaysia. Due to the rapidly expanding need for clinical pharmacokinetics service, it is timely and essential for the Pharmacy Practice & Development Division, Ministry of Health to review and publish this handbook.

This Clinical Pharmacokinetics Pharmacy Handbook 2nd Edition contains the updated and latest information and practice. Besides that, for better understanding in calculation concept and application, the example of real case scenario was included in each of the chapter.

Therefore, I believe the contents of this handbook will help the pharmacist in managing the clinical pharmacokinetics service efficiently. I am confident that this handbook will also provide useful information in ensuring patients receive an optimal and safe treatment based on their individual needs and condition.

Last but not least, I would like to congratulate the Clinical Pharmacy Working Committee (Clinical Pharmacokinetics Subspecialty) for their efforts and contributions in the development of the '*Clinical Pharmacokinetics Pharmacy Handbook 2nd Edition*'

Thank you.

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Clinical Pharmacokinetics Pharmacy Handbook
Second Edition

INTRODUCTION

INTRODUCTION

Clinical Pharmacokinetics Service (CPS) is an extension from of pharmacy service that provides vital roles in patient care and individualization therapy. Initially this services only involved drugs with narrow therapeutic range or/and erratic plasma concentration upon minimal dose manipulation. In Ministry of Health, this service has evolved from only focusing in pharmacokinetic (PK) principal only towards utilizing pharmacokinetics/pharmacodynamics (PK/PD) model in predicting individualized treatment response.

Clinical Pharmacokinetics Pharmacy Handbook 2nd Edition is a revised version of the 2017 publication. It is published by Pharmaceutical Practice & Development Division as a reference material for the purpose of training guidance for pharmacist practising clinical pharmacokinetics in Malaysia. This handbook covers drugs that historically associated with CPS such as aminoglycoside, vancomycin, anti-epileptics, immunosuppressant and toxicology cases. In second edition, there is a new addition in the pre-existing list of drugs requiring therapeutic monitoring, which is Lithium. Therapeutic range for some drugs was also revised according to the latest clinical updates to suit the latest clinical practice, and within the purpose of betterment in patient care provision.

Pharmacokinetics (PKs) described the relationship between administered dose with the drug concentration over the course of time, and is characterized by the systemic input and the disposition kinetic processes. The kinetic processes are commonly referred to as the absorption, distribution, metabolism and elimination of drug (ADME concept). Therapeutic benefit is attained when a drug achieved a given range for efficacy, yet remain below the toxicity threshold. Knowledge in drug PKs is therefore necessary to optimize drug therapy and provide appropriate dose recommendation in populations of interest [1-2]. Clinical pharmacokinetics (CP) is the application of the above

mentioned principles into the clinical practice and patient management, with the intention to produce a safe, effective and individualized pharmacotherapy plan. The primary goal of CP includes optimising effectiveness and minimizing toxicity of patient's drug therapy.

Pharmacodynamics (PDs) refer to the relationship between the presence of drug at the site of action with the resulting effect, which includes the exposure time and intensity of therapeutic and adverse effects. The effect of a drug present at the site of action is determined by the drug's binding affinity with a receptor. The binding of a drug to a receptor generate a direct or a cascade of reaction(s) that will eventually culminate in an observable effect. The concept of PDs is well studied with antibiotics [2]. The emergence of resistance to many antimicrobial agents over the past 10 to 15 years has markedly increase the interest in PDs roles in antimicrobials.

The main challenge faced in managing patient's drug therapy is its variability in individual PK/PD, in which it may influence the design of the dosing regimen. Variability factors that affect pharmacokinetics and pharmacodynamics influence dose regimen design. The rate and degree of absorption of medications administered through routes other than intravenous are highly dependent on the properties of each chemical entity as well as on the environment at the site of administration. Molecular size, solubility, degree of lipophilicity, acid dissociation constant (pKa) and stability are among the important factors influencing the rate and extent of drug absorption. Environmental characteristics that can affect drug absorption include pH, blood flow, surface area, and gastrointestinal motility. In this chapter, we will elaborate the PK/PD changes in special population to facilitate pharmacist in designing the best treatment regime.

DEFINITIONS OF BASIC PHARMACOKINETIC PARAMETERS

A drug's effect is often related to its concentration at the site of action, thus it would be useful to monitor this concentration. However, the site of action are either generally inaccessible for direct observations or the drugs are widely distributed in the body, therefore direct measurement of drug concentration at the sites of action is not practical. Kinetic homogeneity describes the predictable relationship between plasma drug concentration and concentration at the receptor site when a given drug produces its therapeutic effects. Changes in the concentration of drug in plasma directly change the concentration of drug in most tissues proportionally. Table 1 provides common terms and definitions related to pharmacokinetic.

Table 1: Definitions of basic pharmacokinetic parameters

Parameter	Definition
Area under the curve (AUC)	The area under a drug concentration vs time graph
Bioavailability (BA)	The fraction of an administered drug reaching the systemic circulation.
Clearance (CL)	The volume of blood cleared of drug per unit of time.
Half-life ($t^1/_2$)	The amount of time required for the concentration of the drug to decrease by 50%. The half-life is the net effect of all processes leading to removal of the drug.
Elimination rate constant (Ke)	The rate a drug is eliminated from the body per unit of time. The elimination rate constant is inversely proportional to drug half-life.
Extraction ratio	The percentage of medication removed from the blood as it passes through the eliminating organ. The extraction ratio

	depends not only on the blood flow rate but also on the free fraction of drug and the intrinsic ability of the organ to eliminate the drug.
First-pass effect	The process of hepatic metabolism of drugs absorbed from the GI tract as they pass through the liver. First-pass metabolism reduces the amount of drug reaching the systemic circulation, thus reducing bioavailability. First-pass effect only applies to enterally administered medications.
Plasma protein binding	The process by which a drug binds to proteins in the plasma. In general, only free or unbound drugs are available to exert this pharmacologic action or to be distributed, metabolized, or eliminated.
Steady state	A condition when the rate of drug administration is equal to drug elimination. Steady state generally reached after four to five half-lives of a drug. Steady state is a desirable time to evaluate the pharmacologic effect of a drug or to measure serum concentrations. Steady state can also be used to estimate how long it may take for a drug to clear from the body.
Volume of distribution	This is not a physiologic volume but, rather, a theoretical volume that relates the plasma concentration to the administered dose. Medications that are hydrophilic and remain in the central (vascular) compartment, and without high affinity for plasma protein binding, tend to have a lower volume of distribution, with a value that is closer to the intravascular volume. Drugs that are highly lipophilic and distribute to peripheral tissues, or are highly plasma protein bound, tend to have a very large volume of distribution.

Adapted from Smith BS, Yogaratnam D, Lavasseur-Franklin KE, Forni A & Fong J. 2012. Introduction to drug pharmacokinetics in the critically ill patient. *CHEST*. 141(5):1327-1336

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PHARMACOKINETIC CHANGES IN SPECIFIC POPULATION

Pharmacokinetics is typically dependent on a variety of physiological variables (e.g. age, ethnicity, or pregnancy) or pathological conditions (e.g. renal impairment, hepatic impairment, cardiac dysfunction, obesity and others). Nevertheless, the knowledge on the influences of physiological and disease changes on pharmacokinetics parameters can provide pharmacist an insight to predict/optimize drug response while minimizing its toxicity. Careful dose adjustment with routine monitoring of adverse events is necessary in the population with altered PK. In this chapter, we will try to elaborate pharmacokinetic changes in critically ill patients, pediatrics and geriatrics patient with aim to assist pharmacist in interpreting TDM result and optimized patient care generally. These changes are tabulated in table 5.

a) PHARMACOKINETIC CHANGES IN CRITICALLY ILL PATIENTS

In critically ill patients, the major pathophysiological changes that occur may cause alterations in pharmacokinetic of drugs. During critical condition, the balance between the environment at site of administration and the physical properties of drug can significantly different or can significantly differ from normal population. These abnormalities in with the addition to the alterations in distribution, metabolism, and elimination will lead to sub-optimal drug concentration at site of action. These changes are tabulated in table 2.

Table 2: Pharmacokinetic changes in critically ill patients

Parameter	Change	Effect	Example
Absorption	• Perfusion abnormalities • Intestinal atrophy • Delayed gastric emptying • Increased gastric pH due to stress ulcer prophylaxis • Interaction with enteral feeds	• During shock, blood flow is directed to vital organ – reduced blood flow to GI systems. This deprivation reduces the systemic absorption of drugs from GI, intramuscular and subcutaneous tissues. • Reduce in the rate of absorption, T_{max}, C_{max} and onset of the drug effect. • Reduction in AUC of drugs that are weak bases. • Reduction in AUC of selected drugs.	• Significant reduction in the concentration of enoxaparin given subcutaneously [1]. • AUC and T_{max} of paracetamol given orally were significantly reduced in critically ill patients [2]. • Reduced the AUC of weak base drug such as ketoconazole, intraconazole, atazanavir, and dipyridamole [1-2]. • Plasma concentrations of phenytoin have been reported to reduce significantly during enteral feedings [3].
Distribution	• Increase in total body water (TBW) and third space fluid volumes.	• Increase V_d for hydrophilic drugs such as β-lactam antibiotics, which may lead to reduced C_{max} and prolonged half-life and time above MIC if clearance is unchanged. • Possible reduction in efficacy for concentration	• Oedema and substantial fluid administration will increase V_d of hydrophilic drugs [1,4]. • The V_d of gentamicin has been reported to be as large as 0.63L/kg in critically ill patients [1].

		dependent hydrophilic antibiotics.	• The Vd of meropenem, imipenem, piperacillin, cefepime, and ceftazidime was higher in ICU patients as compared to healthy volunteers [5].
	• Decrease in plasma albumin and increase in a1-acid glycoprotein (AAG) as a result of the systemic inflammatory response and other reasons.	• Increase in free fraction of drugs that are highly bind to albumin such as phenytoin. • Reduce in free fraction of drugs that are highly bound to AAG such as lidocaine and tricyclic antidepressants.	• Binding ratio of phenytoin is significantly correlated with albumin levels [2,14]. • Notable 99% increase in clearance of ceftriaxone was observed with the increment in V_d by 32% in patient with hypoalbuminaemia, leading to failure to attain the pharmacodynamics target [6].
	• Alterations in plasma pH	• Increased or reduced the V_d and distribution of drugs dependent on their pKa.	
	• Septic shock • Acute neurological injury associated with inflammation	• Impair distribution of unbound fraction of hydrophilic drugs such as antibiotics in S/C tissues and/or skeletal muscle. • Increased accumulation of free drugs in the CNS,	• The interstitial concentration of piperacillin was reported to be 5 to 10-fold lower than plasma concentration [2]. • Penetration of morphine-3-and 6-glucoronide into CSF

		possibly as a result of down-regulation of BBB efflux transporters (P-gp/MDR1 or MRPs).	increased in proportion to degree of elevation of the pro-inflammatory cytokine IL-6 in CSF [7].
Metabolism	• Hepatic dysfunction	• Hepatic impairment may lead to accumulation of hepatic metabolized drugs.	
	• Reduced hepatic or splanchnic blood flow as a result of shock.	• Reduce hepatic clearance of high extraction drugs.	• During sepsis and septic shock, cardiac output can be increase or decrease, resulting in alterations in hepatic blood flow that leads to reduction of hepatic clearance of high extraction drugs such as metoprolol, midazolam, propranolol, and verapamil [7,14].
	• Hepatic enzyme activity	• Reduce/increase in metabolism of a drug.	• In severe burn injury, the activity of the CYP450 enzymes system can become significantly diminished (phase I metabolism). • Cholestasis, which delays the biliary excretion of drugs, has been found to impair CYP450 function. The inflammatory response associated with trauma, surgery, and haemorrhagic shock

			has been demonstrated to have a variable effect on CYP450. Data suggest that there is a reduction in CYP3A4, 2C19 and 2EI activity while there is an increase in 2C9 activity [14].
Excretion	• Augmented renal clearance (ARC)	• Enhance excretion of circulating metabolites, toxins, waste products, and drug compared to baseline as consequence of glomerular hyper-filtration.	• 63% of patient receiving vancomycin was found to have vancomycin concentration below 10mg/L [8]. • Levetiracetam clearance was higher compared to healthy volunteers [9].
	• Acute kidney injury (AKI)	• The impairment will lead to accumulation of active metabolites that can give toxic effects.	• Accumulation of allopurinol active metabolites (oxypurinol) increase the risk of immune-mediated hypersensitivity [10]. • Accumulation of morphine active metabolites caused CNS depression and respiratory depression [10].

	• Renal replacement therapy (RRT)	• CCVH, CVVHD, CVVHDF, intermittent or SLED may cause removal of drug molecules/metabolites, especially those with high hydrophilicity.	• Significant amount of vancomycin is cleared during CRRT. Standard dosing interval failed to attain the targeted AUC/MIC [11-12]. • A relevant PK variability was observed in critically ill patients receiving meropenem [13].

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b) PHARMACOKINETIC CHARACTERISTICS OF PEDIATRICS

In pediatrics, developmental/physiological changes in absorptive surface can influence the rate and extent of the bioavailability of a drug. Factor including plasma protein binding and water partitioning are continuously fluctuating throughout the first years of life, thus affecting the distribution of drugs. Drug metabolism and elimination vary with age and depends on the substrate or drug. These changes are tabulated in table 3.

Table 3: Pharmacokinetic characteristics of pediatrics

Parameter	Change	Effect	Example
Absorption	• Increase in gastric pH	• Reduce the bioavailability of weak acids drugs. • Increase the bioavailability of weak bases.	• At birth, gastric pH is usually neutral, the pH approximately drops to 1-3 within the first 24 hours of birth. The pH gradually become neutral by day 10 of life. The gastric pH will be similar to adults by the age of 3 years old. Acid labile drugs such as ampicillin, erythromycin, and amoxicillin are more efficiently absorbed when given orally. Weak acid drugs such as phenytoin, paracetamol, and phenobarbital will have low bioavailability [1-5].

	• Increase/delay in gastric emptying time	• Delay absorption of certain drugs	• Gastric emptying time during the neonatal period is prolonged relative to that of the adults. Delayed and incomplete absorption in neonates and small infants have been observed with amoxicillin, rifampicin, phenobarbital, digoxin, and sulphonamides [1,5].
	• Developmental changes in the activity of intestinal drug metabolism enzymes and transporter.	• Increase bioavailability of CYP3A4 substrates • Reduce bioavailability of glutathione S-transferase (GST) substrates	• Immature CYP3A4 in preterm infants has leads to higher bioavailability of oral midazolam.
	• Reduced in intestinal drug transporters expressions/regulations.	• Reduce bioavailability of its substrates	• Gabapentin is absorbed through a L-amino acid transporter in the GI mucosal. This immature transporter had being shown to reduce bioavailability of gabapentin [1,5].

	• Increase in hydration of epidermis	• Increase in absorption of certain drugs	• Topically applied steroid in newborn and infants can result in unpredicted systemic absorption that leads to toxic effects. This is due to better hydration of the epidermis, greater perfusion of the subcutaneous layer, and the larger ration of total BSA to body mass compared to adults [5].
Distribution	• Body water : fat ratio	• Increase volume of distribution of hydrophilic drugs • Reduce volume of distribution of lipophilic drugs	• In premature infants, the total body water is around 80-90% of the total body weight. The extracellular water content is about 45% in neonates compared to 20% in adults. These changes will result in increased Vd of hydrophilic drugs such as gentamicin, vancomycin, linezolid, phenobarbitone and propofol [1]. Higher gentamicin doses per kilogram body weight must be given to adults to achieve comparable plasma

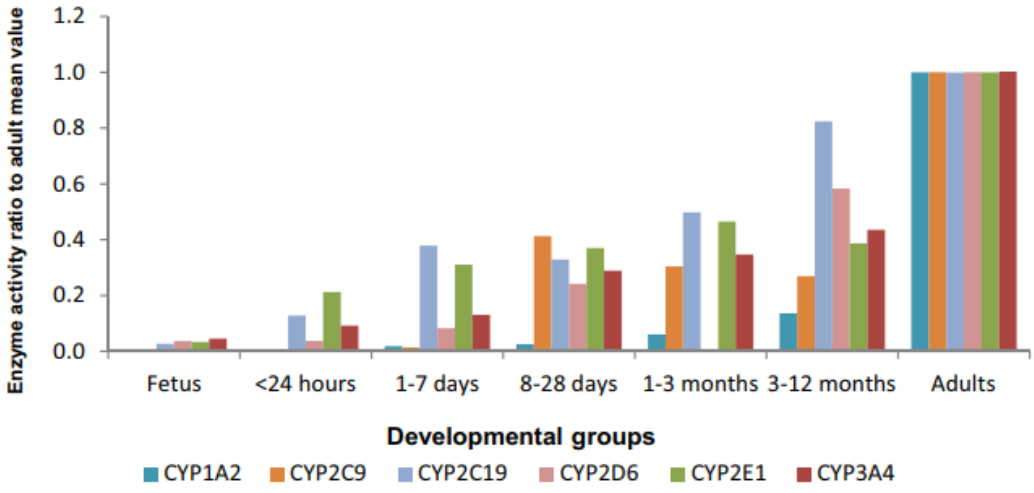
			and tissues concentrations [6]
	• Reduce in protein binding	• Increase in free fraction of highly protein bound drugs	• Greater free fraction of highly protein bound drug such as phenytoin, valproic acid, salicylates, and ampicillin [1,6].
Metabolism	• Reduce in phase I and phase II liver metabolism	• Reduce hepatic clearance	• Developmental change in CYP450 iso-enzymes varies between ages. These developmental changes will influence the metabolism of drugs that used this pathway. The delayed ontogenesis of CYP1A2 is responsible for slow metabolism of theophylline (50%) in neonates compared to adults [1]. • Metabolism clearance of morphine by UGT2B7 is low in neonates and reaches adult levels between 2 and 6 months [6].

Excretion	• Reduce in glomerular filtration rate	• Reduce renal clearance	• The renal excretion of unchanged drug is generally lower in newborns owing to immaturity of renal function [6]. However there is some exception for certain drugs.
	• Reduce in renal tubular absorption and secretion	• Reduced renal clearance	• Renal tubular secretion capacity increases over the first months of life and reach adult level at approximately seven months of age. The renal tubular secretion plays an important role in excretion of digoxin in children and adolescents compared to adult. • The inhibition of renal tubular secretion by amiodarone may cause a steeper increase in serum digoxin concentration in children [1,6].

Table 4: Isoenzyme activity in pediatric population compared to adult with example [5].

Isoenzyme	Pediatrics population activity	Drug class	Examples
CYP1A2	Reduce until 2 years	Antidepressant Bronchodilator	Duloxetine Theophylline
CYP2C9	Reduce until 1-2 years	Anticoagulant Antidepressant NSAIDs	Warfarin Phenytoin Diclofenac, Ibuprofen, Naproxen
CYP2C19	Reduce until 10 years	Antidepressant Benzodiazepine PPIs	Citalopram, Sertraline Diazepam Pantoprazole
CYP2D6	Reduce until 12 years	Analgesic Antidepressant Antihistamine Antipsychotic Beta-blocker	Codeine, Tramadol Amitriptylline, Fluoxetine, Venlafaxine Diphenhydramine Risperidone Labetalol, Metoprolol
CYP3A4	Reduce until 2 years	Analgesic Antiepileptic Antifungal Antihistamine Antiretroviral Benzodiazepines	Fentanyl Carbamazepine Itraconazole, Ketoconazole Loratadine Indinavir,Lopinavir, Ritonavir, Saquinavir Alprazolam, Midazolam
MAO A	Increase until 2 years	-	-
MAO B	Equivalent to adult	-	-
N-Metyltransferases	Equivalent to adult	-	-
UGTs	Reduce until 7-10 years	Analgesic Antiepileptic Benzodiazepine	Morphine Lamotrigine Clonazepam, Lorazepam
NAT2	Reduce until 1-4 years	Antihypertensive Antiinfective	Hydralazine Isoniazid

Figure 1: Developmental profile of major hepatic cytochrome P450s [5]



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c) PHARMACOKINETICS CHANGES IN GERIATRICS

In geriatrics, age-related physiological changes will affect body systems and can alter pharmacokinetic processes in different ways. Subsequently the effects of drugs might be modified.

Table 5: Pharmacokinetics changes in geriatrics

Parameter	Change	Effect	Example
Absorption	• Increase in gastric pH • Delay in gastric emptying • Reduce splanchnic blood flow • Decrease in absorption surface • Reduce in transport protein	• Slightly decrease absorption (rarely clinical significant) • Slightly increase absorption of drug that undergoes first past metabolism • Decrease the bioavailability of pro-drug that needs activation in liver.	• Increased concentration of propranolol and labetalol. • Decreased concentration of ACE inhibitor such as enalapril and perindopril that needs conversion to active metabolites[1,2,6]. • Increased absorption of levodopa due to reduction of dopadecarboxylase in the gastric mucosa[6].
Distribution	• Increase in body fat • Decrease in lean body mass • Decrease in total body water	• Increase Vd and $t^1/_2$ of lipophilic drugs • Increase plasma concentration of hydrophilic drugs - decreased/smaller Vd	• Decreased concentration and prolonged half-life of lipophilic drug such as diazepam, thiopentone, and lignocaine [3,6]. • Increased concentration of water soluble drugs digoxin, lithium ethanol,

			theophylline, and aminoglycosides [4-6].
	• Decrease in serum albumin	• Increase free fraction in plasma of highly protein-bound acidic drugs	• Increased free-fraction of highly albumin bound drug such as phenytoin and ceftriaxone [4].
	• Increase in a1-acid glycoprotein	• Decrease free fraction of basic drugs	• Decreased free fraction of basic drugs such as lignocaine and propranolol [6].
Metabolism	• Decrease in hepatic blood flow	• First-pass metabolism can be less effective	• Reduced clearance of drugs with a high extraction ratio such as glyceryl nitrate, lignocaine, pethidine, and propranolol [6].
	• Decrease in hepatic mass	• Phase I metabolism of some drugs might be slightly impaired; phase II metabolism is restored	• Reduced clearance of drugs metabolized by phase I pathway in the liver (oxidation and reduction) [4,6].
Excretion	• Decrease in renal blood flow • Decrease in glomerular filtration rate	• Renal elimination of drugs can be impaired to a variable extent	• Reduced clearance of water-soluble antibiotics, diuretics, digoxin, water-soluble adrenoceptor blockers, lithium, and NSAIDS. Drug with narrow therapeutic index is likely to cause serious adverse events if they accumulate only marginally more than intended [6].

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Clinical Pharmacokinetics Pharmacy Handbook
Second Edition

AMINOGLYCOSIDE

Aminoglycoside antibiotics include gentamicin, tobramycin, amikacin and streptomycin. Gentamicin is commonly used to treat infections caused by Gram-negative bacilli, Gram positive bacilli and Gram positive cocci, such as *Escherichia coli*, *Proteus* species, *Pseudomonas aeruginosa*, *Serratia* species, *Enterobacter* species, *Citrobacter* species, and *Staphylococcus* species (coagulase-positive and coagulase-negative). Clinical applications of gentamicin include the treatment of infections of the central nervous system (CNS), respiratory, abdominal, urinary systems, bones, skin and soft tissues, endocarditis and septicaemia. It was approved by FDA to be used in combination with ampicillin as empirical therapy for sepsis in newborns and infants. It has also been used for the peritonitis in patients with peritoneal catheters. [14,15]

Amikacin is commonly used for treatment of serious infection (bone and respiratory infections, endocarditis and septicaemia) due to organism resistant to Gentamicin and Tobramycin including *Pseudomonas*, *Klebsiella*, *Enterobacter*, *Serratia*, *Proteus* and *Providencia* species, and *Escherichia coli*. It has also been used for documented infection of susceptible mycobacterial organisms. [14,15]

Target Concentration Range For Selected Aminoglycoside

Dosing	Gentamicin (mg/L)		Amikacin (mg/L)	
	TROUGH	PEAK	TROUGH	PEAK
Neonates[5]	< 1	5 – 12	< 5	20 – 30
MDD [1,2]	<2	5 – 10	<10	20 – 30
SDD [1,2]	< 1	10 – 30*	< 1	60*
Synergy [1]	<1	3 – 5	N/A**	N/A**
Hemodialysis[16,17]	<2	Not necessary	<10	Not necessary

**The target concentration ranges vary and may be individualized based on institutional MIC value to achieve peak to MIC ratio of 10:1.*

***N/A: Not Available*

KEY PARAMETERS:[1,2]

Therapeutic Range	Refer to 'Target concentration range for selected Aminoglycoside'
Bioavailability (F)	Oral: < 10% Intramuscular & Intravenous: ~100%
Volume of Distribution (Vd)	Adult: 0.2 – 0.3 L/kg Pediatrics: 0.3 – 0.5 L/kg
Clearance (CL)	100% unchanged in the urine
Half-life ($t_{1/2}$)	1.5 – 3 hours

PHARMACOKINETICS

Bioavailability:[1]

- Oral: < 10%
- Intramuscular & Intravenous: ~100%

Volume of Distribution (Vd):

Neonates	0.4 – 0.6 L/kg [3]
Pediatrics	0.3 – 0.5 L/kg [1,2]
Adult	0.2 – 0.3 L/kg [1,2]
Obesity (>30% over IBW)	0.26 [IBW + 0.4 (TBW – IBW)] [1]
Cystic fibrosis	0.35 L/kg [1]

Clearance (Cl):[1]

- Elimination: Totally unchanged in the urine.
- Clearance is directly related to renal function
- Hemodialysis clearance: Gentamicin ~50%, Amikacin ~20% (variable; dependent on filter, duration, and type of HD) [14]

Factors that may influence Vd or/and Clearance:[4]

Increase Vd	Ascites, burn patient, cirrhosis, cystic fibrosis, critically ill, pancreatitis, Patent Ductus Arteriosus, post-surgery
Reduce Vd	Dehydration
Increase Cl	Burn patient, cystic fibrosis, dialysis, critically ill
Reduce Cl	Cirrhosis, prematurity, Patent Ductus Arteriosus

Half-life ($t_{½}$):[3]

Neonates (<1 week)	3 – 11.5 hours
Infant (>1 week- 6 months)	3 – 3.5 hours
Adult	1.5 – 3 hours
Adult – Renal failure	50 hours (36 – 72 hours)
Adult – Obese	2 – 3 hours
Burn	1.5 hours

DOSAGE

DOSING STRATEGIES

A. SINGLE DAILY DOSING (SDD)[6]

Based on their concentration-dependent bactericidal action, Aminoglycoside demonstrates more rapid bacterial killing by achieving a high peak concentration approximately ten times the MIC necessary for bacterial growth inhibition [1,2]. Besides that, administration of larger and less frequent doses produce trough concentration lower than assay sensitivity limit (drug free period) between dose intervals which provides:

- Possibly less nephrotoxicity event by decreasing renal cortical Aminoglycoside concentrations. [18]
- Continued suppression of bacterial growth between 2 – 8 hours despite concentration falling below MIC (Post antibiotic effect). [12]

- Less development of adaptive resistance by allowing a recovery period during the dosing interval defined as a recovery period before organisms can resume growth after drug removal. [3]

Due to pharmacokinetic alterations, clinical judgement should be used when using SDD for the following populations:

- Pregnancy (Pregnancy Category D). Only use when benefit outweighs risk.
- Ascites
- Burns
- Gram positive infections (when AMG is used as synergy)
- Creatinine clearance <30 ml/min
- Dialysis
- Neutropenic patients
- Hemodynamically unstable patients
- Cystic fibrosis

Approach 1: SDD Initial Dosing

In general, the adult gentamicin and amikacin dose for SDD in patients with normal renal function is 4 – 7 mg/kg/day and 15 – 20 mg/kg/day respectively. [2] Based on renal function, the initial SDD dose is as follows:

Creatinine Clearance (ml/min)	Dose [7]	
	Gentamicin	Amikacin
> 80	5.1 mg/kg q24h	15 mg/kg q24h
60 – 80	4 mg/kg q24h	12 mg/kg q24h
40 – 60	3.5 mg/kg q24h	7.5 mg/kg q24h
30 – 40	2.5 mg/kg q24h	4 mg/kg q24h
20 – 30	4 mg/kg q48h	7.5 mg/kg q48h
10 – 20	3 mg/kg q48h	4 mg/kg q48h
0 – 10	2 mg/kg q72h & AD*	3 mg/kg q72h & AD*

*AD= after hemodialysis

Approach 2: SDD Initial Dosing based on Hartford Nomogram[6]

Using SDD pharmacodynamics concepts, Hartford method suggests initial use fixed dose of 7 mg/kg of gentamicin and 15 mg/kg of amikacin. The following dosing interval is indicated by the nomogram zone. However, due to utilization of relatively high dose (especially for gentamicin), one should consider suitability of practising this nomogram in local population before its application.

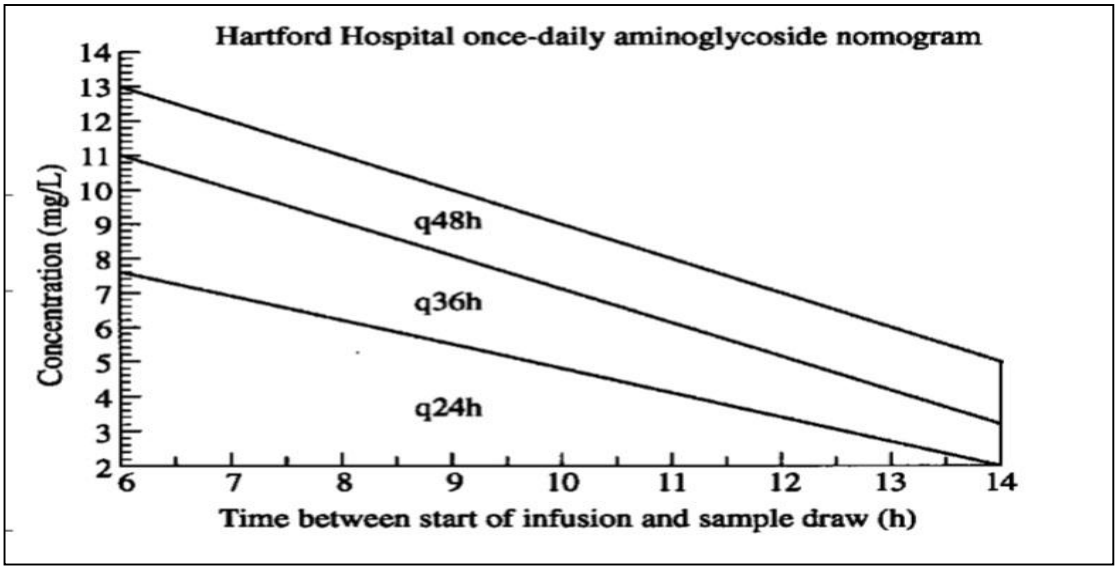

Figure 1.1 Nomogram for concentration monitoring and interval adjustment of gentamicin 7mg/kg & Amikacin 15mg/kg. Take one timed serum concentration taken 6 – 14 hours after dose and plot in the nomogram (divide level by two for amikacin) to determine the dosage interval. If level is above q48h, administer next dose when <1mg/L.

Alternatively, administer 7 mg/kg of gentamicin or 15 mg/kg of amikacin with the following dosage interval. Alter the subsequent dosage interval based on the serum concentration [1] (Refer instruction Figure 1.1)

Creatinine Clearance (ml/min)	Dose interval (hours)
≥60	24
40 – 59	36
20 – 39	48
<20	Monitor serial concentration, re-dose when <1 mg/L

B. CONVENTIONAL DOSING

Conventional dosing is an approach of administering smaller and more frequent doses usually given every 8 – 12 hours or approximately two to three times the half-life.[4] This dosing is commonly given in patients with significant pharmacokinetics alterations as stated in SDD exclusion criteria.[6]

Creatinine Clearance (ml/min)		Gentamicin	Amikacin
>60[8]		1.5 – 2 mg/kg every 8 hourly	5 – 7.5 mg/kg every 8 hourly
40 – 60[8]		1.5 – 2 mg/kg every 12 hourly	5 – 7.5 mg/kg every 12 hourly
20 – 40[8]		1.5 – 2 mg/kg every 24 hourly	5 – 7.5 mg/kg every 24 hourly
<20[8]		1.5 – 2 mg/kg every 48 – 72 hourly*	5 – 7.5 mg/kg every 48 – 72 hourly
RENAL REPLACEMENT DOSING	**HD[3]**	Loading dose: 2 – 3 mg/kg followed by 1 – 2 mg/kg every48 – 72 hourly*	5 – 7.5 mg/kg followed by every 48 – 72 hourly*
	CRRT [3][9]	Loading dose: 3 mg/kg followed by: 2 mg/kg every 24 – 48 hourly*	Loading dose: 10 mg/kg followed by: 7.5 mg/kg every 24 – 48 hourly*
	CAPD[10]	**Intermittent:** IP 0.6 mg/kg daily (1 exchange daily) **Continuous:** LD IP 8 mg/L then MD 4 mg/L in all exchanges	**Intermittent:** IP 2 mg/kg daily (1 exchange daily) **Continuous:** LD IP 25 mg/L then MD 12 mg/L in all exchanges

* Redose when Gentamicin: <2 mg/L (UTI), <3-5 mg/L (G-ve infection) & Amikacin: <10 mg/L

C. SYNERGISTIC DOSING[11,12]

Synergy dosing is a low dose of Aminoglycoside in combination with an antimicrobial agent (i.e. beta-lactams, glycopeptides) against Gram – positive bacterial infections (eg: endocarditis)

CrCl (ml/min)	Dose of Gentamicin
>60	1 mg/kg every 8 hourly
40 – 60	1 mg/kg every 12 hourly
20 – 40	1 mg/kg every 24 hourly
<20	1 mg/kg load*
HD	1 mg/kg every 48 – 72 hourly*
CRRT[9]	1 mg/kg every 24 – 36 hourly*

* Redose when Gentamicin: <1mg/L

AMINOGLYCOSIDE DOSING STRATEGIES –NEONATES[5]

a) Gentamicin

Dosing Chart

PMA (weeks)	Postnatal (days)	Dose (mg/kg)	Interval (hours)
≤29	0 – 7 8 – 28 ≥ 29	5 4 4	48 36 24
30 - 34	0 – 7 ≥ 8	4.5 4	36 24
≥35	ALL	4	24

Suggested Dosing Intervals

Concentration at 24 hours (mg/L)	Half-life (hours)	Suggested Dosing Interval (hours)
≤1	~8	24
1.1 to 2.3	~12	36
2.4 to 3.2	~15	48
≥3.3	-	Measure concentration in 24 hours

b) Amikacin

Postmenstrual Age Dosing Chart [a]

PMA (weeks)	Postnatal (days)	Dose (mg/kg)	Interval (hours)
≤ 29	0 – 7 8 – 28 ≥ 29	14 12 12	48 36 24
30 - 34	0 – 7 ≥ 8	12 12	36 24
≥ 35	ALL	12	24

[a] **Target trough: <8 mg/L, peak: 20-35 mg/L**

Weight Dosing Chart [b]

Weight (g)	Postnatal Age			
	Younger than 14 days		14 days or older	
	Dose (mg/kg)	Interval (hours)	Dose (mg/kg)	Interval (hours)
< 800	16	48	20	42
801-1200	16	42	20	36
1201-2000	15	36	18	30
2001-2800	15	36	18	24
>2800	15	30	18	20

[b] **Target trough: <3 mg/L, peak: >24 mg/L**

Suggested Dosing Intervals

Concentration at 24 hours (mg/L)	Half-life (hours)	Suggested Dosing Interval (hours)
≤ 5	~9	24
5.1 to 8.0	~12	36
8.1 to 10.5	~16	48
≥ 10.6	Not Available	Measure concentration in 24 hours

INTERACTION [3]

Aminoglycoside use with the following drugs/conditions/disease may potentiate toxicity.

Nephrotoxicity	Ototoxicity
Concomitant Drugs	
• Amphotericin B • Cyclosporine • Diuretics (eg: Frusemide) • Other nephrotoxic drugs • Vancomycin	• N/A
Condition/disease	
• Advanced age • Dehydration • Pre-existing renal impairment	• Hearing loss • Tinnitus • Vertigo

SAMPLING

Dosing Type	SDD[2,4,18]	Hartford[6]	Conventional/ Synergistic[2]	Neonates[5]	Dialysis[3]
Initial monitoring	After 1st dose	Single level drawn at 6 – 14 hours post initiation	On 3rd dose	24 hours	18 – 24 hours[13]
Sampling time	Post 2 hours Post 6 hours (Or any two post sampling at least 2 $t_{1/2}$ apart)		Pre: just before/within 30 minutes before the next dose Post: 30 minutes after completion of 30 minutes infusion		Pre HD

MONITORING PARAMETER

- Obtain serum concentrations if there are changes in renal function [11]
- Patient clinical characteristics such as
  - Renal function: creatinine and urea levels[1]
  - Hydration status, input & output fluid balance[1,7]
  - Temperature[1]
  - White blood cell count[1]
- Culture & sensitivity[1]
- Sign and symptoms of auditory or vestibular toxicity[1]

ADVERSE DRUG REACTION

Increase risk of ototoxicity (auditory/vestibular), nephrotoxicity and neurotoxicity (eg: vertigo and ataxia). [3]

DILUTION AND ADMINISTRATION[3]

Dilution of drug:

Amikacin	• Diluent: Normal saline or Dextrose 5% • 500 mg/vial – diluted into 100 – 200 ml of diluent • Concentration: 0.25 – 5 mg /ml
Gentamicin	• Diluent: Normal saline or Dextrose 5% • Diluted into 100 – 200 ml of diluent

Drug administration:

Intravenous Infusion	30 – 60 minutes
Intravenous Bolus	Administer slowly over 2 – 3 minutes
Intramuscular	Administer undiluted into a large muscle mass

CALCULATION

ESTIMATING INITIAL DOSE BASED ON POPULATION PHARMACOKINETICS [2,4]

1. Determine the dosing weight:
   - Determine patient's actual body weight (ABW) in kg
   - Determine patient's ideal body weight (IBW) in kg

$$\text{IBW (Male)} = 50\text{kg} + 0.9(\text{Ht} - 152\text{cm})$$

$$\text{IBW (Female)} = 45.5\text{kg} + 0.9(\text{Ht} - 152\text{cm})$$

   - Compare ABW to IBW
   - Determine to use either ABW, IBW or Adjusted BW for dosing weight based on:

• If ABW/IBW is > 0.9 to < 1.2	=	Use ABW
• If ABW/IBW is > 1.2	=	Use Adjusted body weight
• If ABW/IBW is > 0.75 to < 0.9	=	Use IBW
• If ABW/IBW is ≤ 0.75	=	Use ABW x 1.13

$$\text{Adjusted body weight} = \text{IBW} + 0.4(\text{ABW} - \text{IBW})$$

2. Determine the volume of distribution (Vd):
   (Refer to Vd chart for specific population Vd value)

$$\text{Vd (L)} = \text{Population Vd (L/kg)} \times \text{Dosing Weight (kg)}$$

3. Estimate creatinine clearance (CrCl):

$$\text{CrCL(ml/min)} = \frac{(140 - \text{age}) \times \text{BW(kg)} \times 1.04\ \text{(F) or } 1.23\ \text{(M)}}{\text{Scr } (\mu\text{mol/L})}$$

4. Estimate aminoglycoside clearance(CL_{amg}):

$$\text{CLamg (L/hr)} = \text{CrCl (ml/min)} \times \frac{60\ \text{min}}{1000\ \text{ml}}$$

5. Estimate elimination rate constant (K_e):

$$\text{Ke } (\text{hr}^{-1}) = \frac{\text{CLamg (L/hr)}}{\text{Vd (L)}}$$

6. Estimate half life ($t_{1/2}$):

$$\text{t½ (hr)} = \frac{0.693}{\text{Ke } (\text{hr}^{-1})}$$

7. Estimate dosing interval (τ):

(Round off the interval to logical administration time)

$$\text{Dosing interval, } \tau \text{ (hr)} = \frac{\text{ln target Cmax} - \text{ln target Cmin}}{\text{ke}}$$

8. Estimate initial dose by deciding target Cmax:

$$\text{Initial dose (mg)} = \text{Target Cmax (mg/L)} \times \text{Vd (L)} \times (1 - e^{-K\tau})$$

9. Estimate expected Cmax and expected Cmin concentration:

$$\text{Expected Cmax (mg/L)} = \frac{\text{Dose (mg)}}{\text{Vd (L)} \times (1 - e^{-K\tau})}$$

$$\text{Expected Cmin (mg/L)} = \text{Expected Cmax} \times e^{-K\tau}$$

Cmin	=	Minimum concentration (mg/L)
Cmax	=	Maximum concentration (mg/L)
τ	=	Dosing interval (hour)
mg/L	=	mcg/ml

ESTIMATING NEW DOSE BASED ON PATIENT-SPECIFIC PHARMACOKINETICS [2]

Conventional Dosing: When pre & post concentrations are available

(Both concentrations must have detectable value. For single value/undetectable level please refer to population pharmacokinetic above)

1. Estimate elimination rate constant(K_e):

$$Ke\ (hr^{-1}) = \frac{\ln C2 - \ln C1}{\tau - (t2 - t1)}$$

2. Estimate half-life ($t_{1/2}$):

$$t½\ (hr) = \frac{0.693}{Ke\ (hr^{-1})}$$

3. Estimate C_{max} and C_{min} concentration:

$(\tau' = T\ post - T\ finished\ infusion)$

$$Cmax\ (mg/L) = Cpost \times e^{Ke\tau'}$$

$$Cmin\ (mg/L) = Cmax \times e^{-Ke\tau}$$

4. Determine the volume of distribution (Vd):

$$Vd\ (L) = \frac{Dose\ (mg)}{Cmax(1 - e^{-Ke\tau})}$$

5. Using the calculated Ke, estimate new dose:

$$New\ Dose\ (mg) = Cmax\ (mg/L) \times Vd\ (L) \times (1 - e^{-Ke\tau})$$

$$Cmin\ (mg/L) = Cmax \times e^{-Ke\tau}$$

Cmin	=	Minimum concentration (mg/L)
Cmax	=	Maximum concentration (mg/L)
τ	=	Dosing interval (h)
T	=	Time

Single Daily Dose (SDD): When two post sampling concentrations are available[1]

(Recommended sampling: Post 2 hour (C_2) & post 6 hour (C_6))

1. Estimate elimination rate constant (K_e):

$$Ke\ (hr^{-1}) = \frac{\ln C2 - \ln C6}{t6 - t2}$$

2. Estimate half life ($t_{1/2}$):

$$t½\ (hr) = \frac{0.693}{Ke\ (hr^{-1})}$$

3. Estimate the expected Cmax concentration:
(Used when sample was taken at a time beyond the expected peak, assuming peak concentration occurs 1 hour after start of administration)

$$Cmax = Cpost\ (C2) \times e^{Ket'}$$

4. Estimate the expected Cmin concentration:

$$Cmin = Cmax \times e^{-Ket}$$

5. Determine the volume of distribution (Vd):

$$Vd\ (L) = \frac{Dose\ (mg)}{Cmax\ (1 - e^{-Ket})}$$

6. Calculate the Drug Free Period (DFP):
(Ensure DFP within 2 – 8 hours. If exceeds 8 hours, consider adjust interval/dose)

- First, calculate the time required for Cmax to fall to MIC (tMIC):

$$tMIC\ (hr) = \frac{\ln Cmax - \ln C\ MIC}{Ke}$$

- $DFP\ (hr) = \tau - tmax - tMIC$

Assume tmax =1 (1 hour after start of administration)

C2	=	post 2 hours concentration (mg/L)
C6	=	Post 6 hours concentration (mg/L)
t'	=	Time difference between Cmax and Cpost (hours)
τ	=	Dose interval (hours)
tmax	=	Time of Cmax (hours)
tMIC	=	Time to reach MIC concentration (hours)
Cmax	=	Maximum concentration (mg/L)
CMIC	=	MIC value (mg/L), please use institutional MIC value

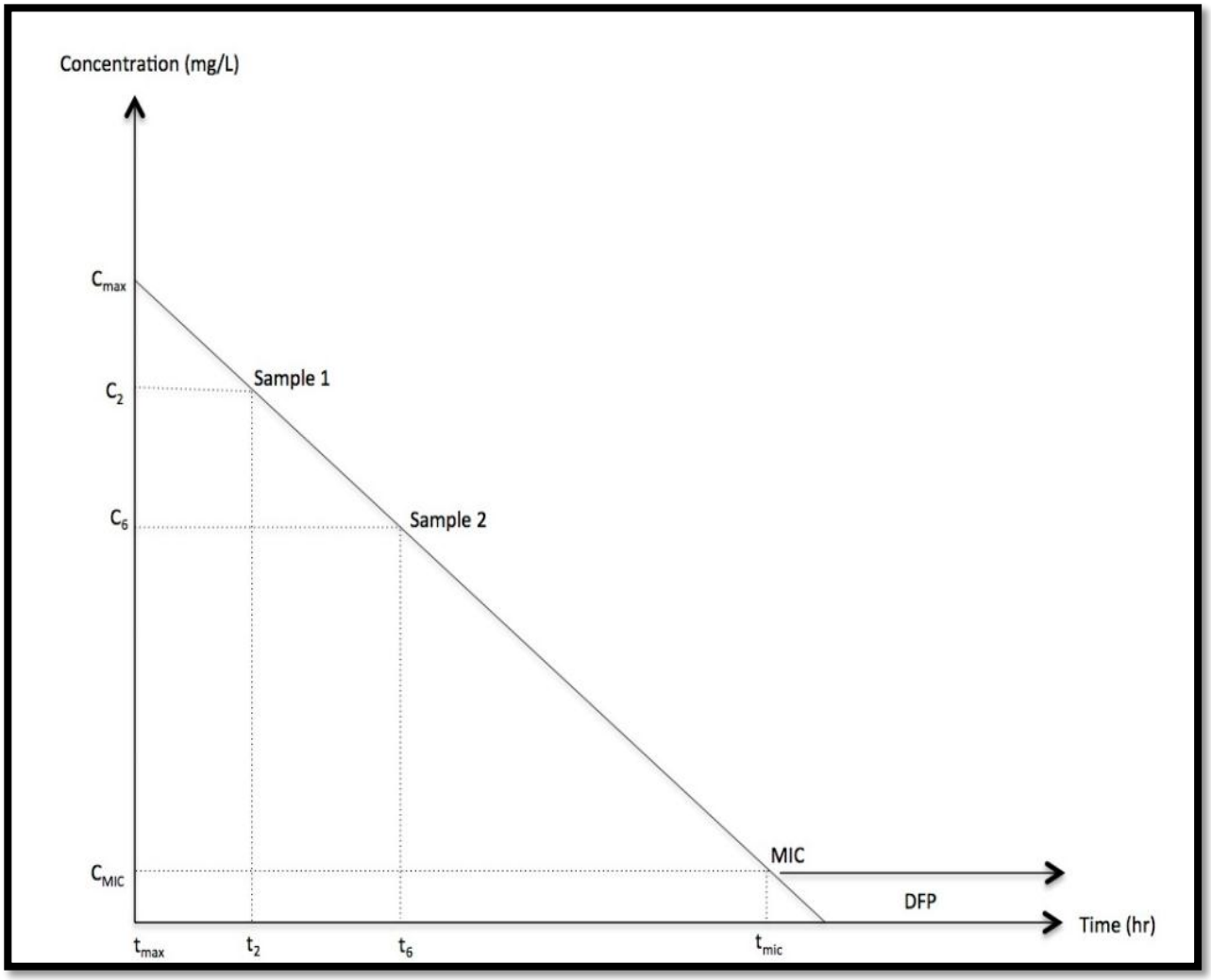

Figure 1.2: Example of two post samplings in SDD monitoring, post 2 hours (sample 1) and post 6 hours (sample 2)

RESULT EVALUATION

CONCENTRATION	RESPONSE	CONTRIBUTING FACTOR	RECOMMENDATION
Subthera-peutic	Poor	• Fluid overload • Ascites	➢ Correct the fluid imbalance (if fluid overload), increase the dose appropriately & resample
		• Wrong sampling time	➢ Repeat another sample for confirmation
		• Insufficient dose	➢ Increase the dose appropriately & resample
		• Drug interaction	➢ Use alternative drug if possible, if unavoidable, increase the dose appropriately & resample
		• Burn	➢ Increase the dose appropriately (use conventional dosing) & resample
	Good		➢ Continue current dose
Within normal therapeutic range	Poor		➢ If sampling time is satisfactory & hydration status is fair, increase the dose (not more than max recommended)
	Good		➢ Continue current dose
Potential Toxic/ Toxic	Toxic effect: • Nephro-toxicity • Oto-toxicity	• Dehydration • Over dosage • Underlying disease/ factors	➢ Withhold treatment (if necessary), hydrate the patient (if dehydrated) then reduce dose accordingly
		• Renal failure	➢ Withhold treatment then reduce dose accordingly
		• Possible drug interaction	➢ Use alternative drug if possible, if unavoidable, withhold treatment (if necessary) then reduce dose accordingly

The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic parameter and clinical condition should be considered before making any recommendations.

CASE DISCUSSION

Case 1:

ABC (45 years old male, 175 cm, 130 kg) was diagnosed with Hospital-acquired pneumonia (HAP) and was in septic shock. Tracheal C&S innoculated *Pseudomonas aeruginosa*. IV Cefepime 2g TDS was started for HAP. Doctor would like to add IV Amikacin as dual therapy. What is your recommendation for Amikacin starting dose?

Lab values: Urea=4.0 mmol/L, Scr =110 µmol/L, WBC=25x10^9/L, CRP=213 mg/L

1. Determine the dosing weight:

Actual BW (ABW) =130 kg

Ideal BW (IBW) = 50 kg + 0.9 (175 – 152 cm)

= 70.7 kg

ABW/IBW =1.84 (>1.2 use Adjusted BW)

Adjusted BW = 70.7 + 0.4 (130 - 70.7)

= 94.42 kg

2. Determine the volume of distribution (Vd):

Vd = 0.26 x 94.42

= 24.55 L

3. Estimate creatinine clearance (CrCl):

$$CrCL = \frac{(140 - 45) \times 94.42 \times 1.23}{110}$$

=100.30 ml/min

4. Estimate aminoglycoside clearance(CL_{amg}):

$$CL_{amg} = 100.30 \times \frac{60}{1000}$$

= 6.018 L/hr

5. Estimate elimination rate constant (K_e):

$$K_e = \frac{6.018}{24.55}$$

= 0.245 hr^{-1}

6. Estimate half life ($t_{1/2}$):

$$t_{1/2} = \frac{0.693}{0.245}$$

$$= 2.83 \text{ hr}$$

7. Estimate dosing interval (τ):

(Round off the interval to logical administration time)

$$\text{Dosing interval, } \tau = \frac{\ln 30 - \ln 2}{0.245}$$

$$= 11.05 \text{ hr } (\sim 12 \text{ hr})$$

8. Estimate initial dose by deciding target Cmax:

$$\text{Initial dose} = 30 \times 24.55 \times [1 - e^{-0.245(12)}]$$

$$= 697 \text{ mg}$$

$$\sim 750 \text{ mg (round up to nearest 250mg's)}$$

9. Estimate expected Cmax and expected Cmin concentration:

$$\text{Cmax} = \frac{750}{24.55 \times [1 - e^{-0.245(12)}]}$$

$$= 32.25 \text{ mg/L}$$

$$\text{Cmin} = 32.25 \times e^{-0.245(12)}$$

$$= 1.70 \text{ mg/L}$$

Recommendation of starting dose: IV Amikacin 750 mg BD.

Suggest checking pre- and post-level on third dose for therapeutic monitoring.

Case 2:

DEF, term neonate (5 days of life, 50 cm, 3.2 kg) was treated as neonatal sepsis. IV C-Penicillin 320,000u BD and IV Gentamicin 12.8 mg OD was started. First dose of IV Gentamicin was given on 1/1/19, 12 pm (30 minutes infusion). Gentamicin pre and post samples were taken on 2nd dose.

Lab values: Urea=5.0 mmol/L, Scr=60 µmol/L, WBC=15x10^9/L, CRP=0.6 mg/L

TDM results as follows:

Gentamicin	Sampling Time	Gentamicin Concentration
Pre sample	2/1/19, 11:30 am	1.5 mg/L
Post sample	2/1/19, 1:00 pm	9.8 mg/L

1. Estimate elimination rate constant(K_e):

$$Ke = \frac{\ln 9.8 - \ln 1.5}{24-(1.5)}$$

$$= 0.083\ hr^{-1}$$

2. Estimate half-life ($t_{1/2}$):

$$t_{1/2} = \frac{0.693}{0.0834}$$

$$= 8.35\ \text{hours}$$

3. Estimate peak, (C_{max}) and trough (C_{min}) concentration:
($\tau' = \text{T post} - \text{T finished infusion}$)

$$Cmax = 9.8 \times e^{0.083\,(0.5)}$$

$$= 10.22\ mg/L$$

$$Cmin = 10.22 \times e^{-0.083(24)}$$

$$= 1.39\ mg/L$$

4. Determine the volume of distribution (Vd):

$$Vd = \frac{12.8}{10.22 \times [1 - e^{-0.083(24)}]}$$

$$= 1.45\ L$$

5. Using the calculated Ke, estimate new dose:

Pre level higher than targeted concentration of 1 mg/L, indicated clearance is poor, hence dosing interval should be prolonged.

Decide a longer dosing interval* and expected Cmax, then calculate new dose.

*Based on Aminoglycoside Dosing Strategies – Neonates[5], suggested dosing intervals as follows:

Concentration at 24 hours (mg/L)	Half-life (hours)	Suggested Dosing Interval (hours)
≤ 1	~8	24
1.1 to 2.3	~12	36
2.4 to 3.2	~15	48
≥ 3.3	-	Measure concentration in 24 hours

Suggested dosing interval is 36 hours for pre level of 1.5 mg/L. If maintain the target Cmax around 10 mg/L, new dose is calculated as followed:

$$\text{New Dose} = 10 \times 1.45 \times [1 - e^{-0.083(36)}]$$
$$= 13.8 \text{ mg}$$

$$\text{Expected Cmin} = 10 \times e^{-0.083(36)}$$
$$= 0.50 \text{ mg/L}$$

Recommendation of new dose: IV Gentamicin 13.8 mg 36 hourly starting at 12am on 4/1/19 in order to achieve a Cmax of 10 mg/L and Cmin of 0.50 mg/L. Recheck pre- and post-level on 5/1/19 at 11:30 am and 1:00 pm for therapeutic monitoring if plan to continue Gentamicin treatment for one week or more. Otherwise, no need recheck level if plan to complete 5 days treatment.

Case 3:

GHI (24 years old male, 176 cm, 64 kg) was diagnosed with pyelonephritis. Urine and pus C&S showed *Pseudomonas aeruginosa* sensitive to Gentamicin (MIC=0.5 mg/L). Doctor prescribed IV Gentamicin 240 mg OD for him. Post 2 hours sample and post 6 hours sample were drawn after 2nd dose of IV Gentamicin at 5/1/19, 12 pm. Infusion time for Gentamicin was 1 hour.

Lab values: Urea=2.2 mmol/L, Scr=76 µmol/L, WBC=15x10^9/L, CRP=60 mg/L

TDM results as follows:

Gentamicin	Sampling Time	Gentamicin Concentration
Post 2 hours sample	5/1/19, 2 pm	12.2 mg/L
Post 6 hours sample	5/1/19, 6 pm	4.8 mg/L

1. Estimate elimination rate constant (K_e):

$$Ke = \frac{\ln 12.2 - \ln 4.8}{4}$$
$$= 0.233\ hr^{-1}$$

2. Estimate half life($t_{1/2}$):

$$t_{1/2} = \frac{0.693}{0.233}$$
$$= 2.97\ \text{hours}$$

3. Estimate the expected Cmax concentration:
(Used when sample was taken at a time beyond the expected max, assuming max concentration occurs 1 hour after start of administration)

$$Cmax = 12.2 \times e^{0.233(1)}$$
$$= 15.40\ mg/L$$

4. Estimate the expected C_{trough} concentration:

$$Cmin = 15.40 \times e^{-0.233(24)}$$
$$= 0.06\ mg/L$$

5. Determine the volume of distribution (Vd):

$$Vd = \frac{240}{15.40 \times [1 - e^{-0.233(24)}]}$$

= 15.64 L

6. Calculate the Drug Free Period (DFP):
(Ensure DFP within 2 – 8 hours. If exceeds 8 hours, consider adjust interval/dose)

- First, calculate the time required for Cmax to fall to MIC (tMIC):

$$tMIC = \frac{\ln 15.40 - \ln 0.5}{0.233}$$

= 14.7 hours

DFP = 24 – 1 – 14.7
= 8.3 hours

DFP slightly exceeds 8 hours, consider adjust dose/interval.

If increase dose to 320 mg OD (5 mg/kg),

$$\text{Expected Cmax} = \frac{320}{15.64 \times [1 - e^{-0.233(24)}]}$$

= 20.54 mg/L

Expected Cmin = 20.54 x $e^{-0.233(24)}$
= 0.08 mg/L

$$tMIC = \frac{\ln 20.54 - \ln 0.5}{0.233}$$

= 15.9 hours

DFP = 24 – 1 – 15.9
= 7.1 hours

DFP less than 8 hours, consider giving 320 mg OD.

Recommendation of new dose: IV Gentamicin 320 mg OD starting at 12pm on 6/1/19 in order to achieve a Cmax of 20.54 mg/L and Cmin of 0.08 mg/L. Recheck post 2 hours and post 6 hours level on 7/1/19 at 2 pm and 6 pm for therapeutic monitoring if plan to continue gentamicin treatment for one week or more. Otherwise, no need recheck level if plan to complete 5 days treatment.

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Clinical Pharmacokinetics Pharmacy Handbook
Second Edition

CARBAMAZEPINE

Carbamazepine is an iminostilbene derivative[1] that is structurally similar to the tricyclic antidepressant agents. [1,2] It has FDA approval for generalized tonic-clonic (grand mal) and partial (psychomotor, temporal lobe) seizures, trigeminal and glossopharyngeal neuralgia syndromes, bipolar I disorder, and in acute mania and mixed episodes. It is also used in other conditions including pain syndromes, migraine headaches, neurologic disorders and schizophrenia. [2]

Due to the lack of an intravenous dosage form, thus, Carbamazepine is used primarily in the chronic therapy of epilepsy. [2] It is ineffective in absence or myoclonic seizures and can worsen or precipitate absence seizures. [3]

The antiseizure mechanism of carbamazepine is to reduce the transmission in the nucleus ventralis anterior section of the thalamus; inhibition of voltage-gated sodium channels and it also depresses post-tetanic potentiation and prevents increases in cyclic adenosine monophosphate (cAMP). [1]

Carbamazepine carries a black-box warning on serious dermatologic reactions (especially in Asian population of genetically inherited with HLA-B*1502 allele), aplastic anemia, and agranulocytosis. Besides that, Carbamazepine used also associated with severe dermatologic reaction includes TEN (toxic epidermal necrolysis) and SJS (Steven-Johnson syndrome). [2]

KEY PARAMETERS:

Therapeutic Range [2,3,5]	4 – 12 mg/L
Bioavailability (F) [3]	0.85 – 0.9
Salt Factor (S) [2]	1.0
Volume of Distribution (Vd) [2,3]	Neonates: 1.5 L/kg Pediatric: 1.9 L/kg Adults: 0.6 – 2L/kg (average ~1.4L/kg) (Based on actual body weight)
Clearance (CL) [2]	Monotherapy: 0.064 L/kg/hr Polytherapy: 0.10 L/kg/hr Pediatric (monotherapy): 0.11 L/kg/hr
fu (fraction unbound in plasma) [2]	0.2 – 0.3
Half-life ($t_{1/2}$) [2]	Pediatric: 4 – 12 hours Adult monotherapy: 15 hours Adult polytherapy: 10 hours

PHARMACOKINETIC

Absorption:[2]

Bioavailability (F): Oral (Immediate release tablets, controlled release tablets and oral suspension): 80%

Distribution: [2,3]

- Volume of Distribution (Vd):

Neonates	1.5 L/kg
Pediatric	1.9 L/kg
Adults	0.6– 2 L/kg (average ~1.4 L/kg)

(Based on actual body weight)

- Carbamazepine distributes rapidly and uniformly to various organs and tissues, achieving higher concentrations in organs of high blood flow (e.g. liver, kidney and brain) [3]
- The concentration of carbamazepine in breast milk is about 25 – 60% of concentration of mother's plasma. [3]
- Carbamazepine rapidly crosses the placenta and accumulates in fetal tissue (it is in pregnancy category class D). [2]
- Carbamazepine binds to both albumin and to alpha-1-acid glycoprotein (AGP). [1] In normal patients, plasma protein binding is 75% - 80% resulting in a free fraction of drug of 20% - 25%. [1]
- The concentration of AGP and the free fraction of carbamazepine may vary with the presence of inflammation, trauma, concurrent antiepileptic drug therapy and age. [3]

Metabolism: [2,3]

Carbamazepine is metabolized primarily by the P450 isozyme CYP 3A4 and induces CYP 1A2, CYP 2C9, and CYP 3A4 to accelerate the hepatic metabolism of other drugs. It is about 99% metabolized by oxidation, hydroxylation, direct conjugation with glucuronic acid, and sulphur conjugation pathways. The most important metabolite is 10,11-epoxide, which appears to be active and may contribute to the efficacy and toxicity of carbamazepine.

Elimination: [2]

Carbamazepine is eliminated almost exclusively by the metabolic route, with less than 2% of an oral dose being excreted unchanged in the urine.

Adult Monotherapy	0.064 L/kg/hr
Adult Polytherapy	0.10 L/kg/hr
Pediatric (monotherapy)	0.11 L/kg/hr

The increase in clearance associated with chronic therapy is apparently due to auto-induction of its metabolic enzymes.

AUTOINDUCTION: [1]

- Carbamazepine induced its own metabolism via the hepatic microsomal enzyme CYP3A4 system. (onset is as early as 24 hours, and the time to completion has been reported to range from 1 to 5 weeks)
- When dosing is initiated, serum concentrations increase according to the baseline clearance and half-life.
- After a few doses of carbamazepine, enough auto-induction has occurred that clearance increases, half-life decreases and drug accumulation slows down.
- With additional exposure of liver tissue to carbamazepine, clearance continues to increase and half-life continues to shorten.
- As a result, concentration decline and ultimately stabilize in accord with the new clearance and half-life values.
- Thus, for initial dose, patient are started on ¼ - ⅓ of the desired maintenance dose to avoid side effects of early therapy and taper up similar amount every 2-3 weeks until the total desired daily dose.

Half Life ($T_{½}$):

The half-life changes with continued dosing and is affected by other drugs. [3]

Pediatric	4 – 12 hours [2]
Adult monotherapy	15 hours[2]
Adult polytherapy	10 hours[2]

Indication and Therapeutic range:

Bipolar disorder	4 – 12 mg/L [1,2,3,5]
Epilepsy	
Trigeminal neuralgia	

DOSAGE

Pediatric[9]

Epilepsy:

Child 1 month – 12 years:

Initially 5 mg/kg at night or 2.5 mg/kg twice daily, increased as necessary by 2.5 – 5 mg/kg every 3 - 7days; usual maintenance dose 5 mg/kg 2 - 3 times daily; doses up to 20 mg/kg daily have been used.

Child 12-18 years:

Initially 100 – 200 mg 1 - 2 times daily, increased slowly to usual maintenance dose 200 mg – 400 mg 2 – 3 times daily; in some cases doses up to 1.8 g daily may be needed

Adult[7]

Epilepsy:

Initial: 400 mg/day in 2 divided doses (tablets or extended release tablets) or 4 divided doses (oral suspension)

Maintenance: Increase by up to 200 mg/day at weekly intervals using a twice daily regimen of extended release tablets, or a 3 – 4 times daily regimen of other formulations until optimal response and therapeutic concentrations are achieved; usual dose: 800 – 1200 mg/day

Maximum: 1600 mg/day; however, some patients have required up to 2400 mg/day

Bipolar disorder:

Initial: 400 mg/day in two divided doses (tablets or extended release tablets) 4 divided doses (oral suspension)

Maintenance: May adjust by 200 mg/day increments

Maximum: 1600 mg/day

Trigeminal or glossopharyngeal neuralgia:

Initial: 200 mg/day in 2 divided doses (tablets or extended release tablets) or 4 divided doses (oral suspension) with food, gradually increasing in increments of 200 mg/day as needed

Maintenance: 400 – 800 mg daily in 2 divided doses (tablets or extended release tablets) or 4 divided doses (oral suspension)

Maximum: 1200 mg/day

Special Population:

a) Renal Impairment:[7]

Infants, Pediatric and Adolescents:

- GFR ≥10 ml/minute/1.73m^2: No dosage adjustment required
- GFR <10 ml/minute/1.73 m^2: Administer 75% of normal dose
- Intermittent haemodialysis: Administer 75% of normal dose; on dialysis days give dose after haemodialysis
- Peritoneal dialysis (PD): Administer 75% of normal dose
- Continuous renal replacement therapy (CRRT): Administer 75% of normal dose; monitor serum concentrations

Note: Renally adjusted dose recommendations are based on doses of 10-20 mg/kg/day divided every 8-12 hours.

Adults:

- GFR ≥10 ml/minute: No dosage adjustment required
- GFR <10 ml/minute: Administer 75% of dose
- Intermittent haemodialysis: Administer 75% of normal dose; on dialysis days give dose after haemodialysis
- Peritoneal dialysis (PD): Administer 75% of normal dose
- Continuous renal replacement therapy (CRRT): No dosage adjustment recommended

b) Hepatic Impairment:[2]

Patient with liver cirrhosis or acute hepatitis have reduced carbamazepine clearance because of destruction of liver parenchyma. This loss of functional hepatic cells reduces the amount of CYP3A4 available to metabolize the drug and decreases clearance.

Carbamazepine serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with liver cirrhosis.

Carbamazepine has many drug interactions resulting both from CYP3A4 inhibition and CYP3A4 induction which alter observed concentrations. [1]

CYP 3A4 **inhibitors** which inhibit carbamazepine metabolism and increase carbamazepine plasma concentration include	CPY 3A4 **inducers** which induce the rate of carbamazepine metabolism and decrease carbamazepine plasma concentration include
Increased Plasma Carbamazepine	**Decreased Plasma Carbamazepine**
Clarithromycin Diltiazem Erythromycin Fluoxetine Grapefruit juice Isoniazid Loratadine Valproate Verapamil Azole antifungals: Fluconazole,Itraconazole, Ketoconazole Protease inhibitors: Indinavir, Nelfinavir, Ritonavir	Cisplatin Doxorubicin Phenobarbital Phenytoin Primidone Rifampicin Theophylline Carbamazepine (autoinduction)

SAMPLING

Time to monitor serum concentration (at steady state)

The time to steady state depends on the completion of auto-induction.[2]

i. Initiation:

After an initial dose, CBZ takes 2 – 3 weeks to achieve steady state. Dose adjustment is not recommended during this period. [1]

ii. After initiation (2 – 3weeks) and dose adjustment:

After dose adjustment, CBZ takes 2 – 5 days to achieve steady state [8]

Sampling Time

Pre-sample or trough concentration taken: just before next dose after steady state achieved [1]

MONITORING PARAMETER[3]

- Carbamazepine blood concentrations; periodically to optimize efficacy and reduce toxicity
- Complete blood count, including platelets and differential; before initiating therapy and periodically thereafter
- Hepatic function tests, especially in patients with a history of liver disease; prior to initiation of therapy and periodically thereafter
- Complete urinalysis and BUN determinations; baseline and periodically during therapy
- Improvement in seizure control may be indicative of efficacy
- Reduction in pain of trigeminal neuralgia and other neurological syndromes may indicate efficacy
- Improvement in symptoms of bipolar disorder may indicate efficacy

ADVERSE DRUG REACTION

Common [5]

Cardiovascular	Hypotension
Dermatologic	Pruritus (8%), rash (7%)
Gastrointestinal	Constipation (10%), nausea (29%), vomiting (18%), xerostomia (8%)
Neurologic	Asthenia (8%), ataxia (15%), dizziness (44%), somnolence
Ophthalmic	Blurred vision (6%), nystagmus

Serious [5]

Cardiovascular	Atrioventricular block, cardiac dysrhythmia, congestive heart failure, eosinophilic myocarditis, hypersensitivity, syncope
Dermatologic	Stevens-Johnson syndrome, toxic epidermal necrolysis
Endocrine metabolic	Hypocalcemia, hyponatremia (4% to 21.7%), water intoxication syndrome
Gastrointestinal	Pancreatitis
Hematologic	Agranulocytosis, aplastic anaemia, bone marrow depression, eosinophilia, leukopenia, pancytopenia, thrombocytopenia
Hepatic	Hepatitis, hepatotoxicity, liver failure, vanishing bile duct syndrome
Immunologic	Drug hypersensitivity syndrome
Neurologic	Acute intermittent porphyria
Renal	Azotemia, renal failure
Respiratory	Pulmonary hypersensitivity
Other	Angioedema

Overdosage/Toxicology:[5]

Poisoning is common and there are several deaths each year from carbamazepine poisoning.

Peak serum concentration less than 30 mg/L are generally associated with mild to moderate toxicity. Peak serum concentration more than 40 mg/L may be associated with coma, seizures and hypotension.

Management of overdosage/toxicology:

- Supportive care is mainstay treatment
- Activated charcoal may be considered in asymptomatic patients who are likely to have medication remaining in their GI tract, or in symptomatic patients who have a secure airway. Whole bowel irrigation may be considered for patients with severe toxicity involving ingestion of a large amount of a sustained release formulation. Gastric lavage may be considered for very large overdoses presenting early.
- Antidote: none
- Haemoperfusion or high flux haemodialysis may be useful in severe, life-threatening overdose.
- Monitor Carbamazepine serum concentration every 4 hours until the concentration has peaked and is clearly declining.

DILUTION AND ADMINISTRATION[7]

Drug Administration:

To be taken with food.

Controlled Release tablet: Swallow whole, do not chew/crush.

CALCULATION

A) Dose Initiation

Maintenance dose: Oral

1. Estimate clearance (CL) :

   (Refer to CL chart for specific population CL value)

$$\text{CL (L/hour)} = \text{CL (L/kg/hour)} \times \text{BW (kg)}$$

2. Determine C_{ss} target (4 – 12 mg/L) & calculate the maintenance dose

$$\text{MD(mg)} = \frac{\text{CL(L/hour)} \times \text{Css target (mg/L)} \times \text{Interval (hour)}}{\text{S} \times \text{F}}$$

B) Dose Adjustment

1. Estimate CL from the obtained concentration

$$\text{CL (L/hour)} = \frac{\text{S} \times \text{F} \times \text{Dose(mg)}}{\text{Interval (hour)} \times \text{Css (mg/L)}}$$

2. Determine Css target and calculate the new maintenance dose

$$\text{MD(mg)} = \frac{\text{CL(L/hour)} \times \text{Css target (mg/L)} \times \text{Interval (hour)}}{\text{S} \times \text{F}}$$

RESULT EVALUATION

CONCENTRATION	RESPONSE	CONTRIBUTING FACTOR	RECOMMENDATION
Subtherapeutic < 4 mg/L	**Poor** **Good**	• **Compliance** • **Wrong sampling time** • **Insufficient dose** • **Drug Interaction**	• **If compliance & sampling time is satisfactory, increase the dose appropriately & re-sample after 5 days** • **Continue current dose**
Within normal therapeutic range 4 – 12 mg/L	**Poor** **Good**	• **Insufficient dose** • **Drug Interaction**	• **If compliance & sampling time is satisfactory, increase the dose (not more than max. recommended)** • **Continue current dose**
Potential toxic/ Toxic **> 12 mg/L**	**Toxic effect:** • **Diplopia** • **Hyponatremia** • **Seizure** • **Arrythmia** • **Dizziness**	• **Overdosage** • **Underlying disease/ factors** • **Possible drug interaction**	• **Withhold treatment, monitor concentration and treat signs & symptoms of toxicity (if required), then adjust dose accordingly**

The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic parameter and clinical condition should be considered before making any recommendations.

CASE DISCUSSION

Case 1

L.J.Q., a 25-years-old, 50 kg female, diagnosed with complex partial seizure since 8 months old. After failure in previous anticonvulsant treatment, her neurologist has planned to start her with carbamazepine as a new anticonvulsant agent. How would you initiate the therapy? Explain your rationale. Estimate amount needed at steady state and then propose how to start the patient on therapy. Calculate a daily dose that will produce an average steady-state plasma concentration of approximately 6 mg/L.

Bioavailability (F) = 0.8

Average clearance (CL) = 0.064 L/kg/hr X 50kg = 3.2 L/hr

Salt factor (S) = 1.0

$$\text{MD(mg)} = \frac{\text{CL (L/hour)} \times \text{Css target (mg/L)} \times \text{Interval (hour)}}{\text{S} \times \text{F}}$$

$$= \frac{(3.2\ \text{L/hr}) \times (6\ \text{mg/L}) \times (24\ \text{hr/day})}{(1) \times (0.8)}$$

$$= 576\ \text{mg/day}\ (\sim 600\ \text{mg/day})$$

Calculated dose will be rounded up to approximately 600 mg/day in order to achieve the estimated steady-state concentration of 6 mg/L after autoinduction of carbamazepine metabolism had taken place. Thus, carbamazepine should be started on a lower daily dose initially at 1 to 2 weeks intervals based on her clinical response. Usual initial daily dose for adult patients is 200 mg to 400 mg with increment of approximately 200 mg every 1 to 2 weeks.

Case 2

L.J.Q. was discharged with carbamazepine dose of 200 mg BID and the dose was increase to 300 mg BID 3 weeks later. After 1 month, patient was arranged for a follow-up in neuromedical clinic. On current regimen, patient claimed that though there is a reduction in seizure frequency but overall control was not satisfactory. The steady-state carbamazepine concentration during this visit was reported to be 4.8 mg/L. What dose would be required in order to achieve a new steady state carbamazepine concentration of 6 mg/L?

$$\text{CL (L/hour)} = \frac{\text{S} \times \text{F} \times \text{Dose(mg)}}{\text{Interval (hour)} \times \text{Css(mg/L)}}$$

$$= \frac{(1) \times (0.8) \times (300 \text{ mg/12hr})}{4.8 \text{ mg/L}}$$

$$= 4.2 \text{ L/hr}$$

$$\text{MD(mg)} = \frac{\text{CL (L/hour)} \times \text{Css target (mg/L)} \times \text{Interval (hour)}}{\text{S} \times \text{F}}$$

$$= \frac{(4.2 \text{ L/hr}) \times (6 \text{ mg/L}) \times (24 \text{ hr/1day})}{(1) \times (0.8)}$$

$$= 756 \text{ mg/day } (\sim 800 \text{ mg/day})$$

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Clinical Pharmacokinetics Pharmacy Handbook
Second Edition

CYCLOSPORINE

Cyclosporine is a cyclic polypeptide with immunosuppressant properties that is used for the prevention of graft-versus-host disease in bone marrow transplant patients, for the prevention of graft rejection in solid-organ transplant patients and for the treatment of psoriasis, rheumatoid arthritis, and various autoimmune disorders. It works by decreasing the activity of the immune system.

KEY PARAMETER :

Therapeutic Range	C_0 ~ 100 – 500 mcg/L C_2 ~ 600 – 1700 mcg/L
Bioavailability (F)	Oral: 30%
Salt Factor (S)	1
Volume of Distribution (Vd)	3 – 5 L/kg
Clearance (CL)	5 – 10 ml/kg/min
Half-life ($t_{1/2}$)	8.4 hours (ranges 5 – 18 hours)

PHARMACOKINETIC

Bioavailability (F):

- Oral Cyclosporine (modified) - bioavailability of capsule and oral solution are equivalent.
- Pediatric (1 – 10 years): 43% (range 30 – 68%) [1,4]
- Adult: Approximately 30%[1-3]

Volume of Distribution (Vd):

- Cyclosporine is widely distributed in tissues and body fluids including the liver, pancreas and lungs; also crosses placenta and enters breast milk. [1]
- The volume of distribution is 3 – 5 L/kg. [2,3,4]
- The relatively large Vd is due to cyclosporine significantly bound to plasma and blood elements that is probably tissue outside the vascular phase. [2]
- Protein Binding: 90 – 98% to lipoproteins. [1]

Clearance (CL):

Cyclosporine is primarily by hepatic metabolism via CYP3A4. [1]

Oral	0.42 – 0.48 L/kg/h (7 – 8 ml/kg/min)[2,3]
Intravenous	0.30 – 0.42 L/kg/h (5 – 7 ml/kg/min)[2,3]

* Pediatric may have higher clearance; 10 – 15 ml/kg/min [3]

For patient with liver failure; 3 ml/kg/min [1]

Half-life ($t_{½}$):

- Generally, half life of Cyclosporine is around 8.4 hours (ranges 5-18). [1-3]
- Half-life of cyclosporine may be prolonged in patients with liver failure (20 hours) and shorter in pediatric (6 hours) due to the higher metabolic rate. [1,5]

Indication and Therapeutic Range:

Cyclosporine inhibits production and release of interleukin II and inhibits interleukin II-induced activation of resting T-lymphocytes. [1]

Cyclosporine is indicated for:

- Patients in whom donor specific transplantation cannot be carried out and in young children to minimize side effects of steroids.
- Bone marrow transplant
- Solid organ transplant
- Severe rheumatoid arthritis not responding to other second line drugs
- Idiopathic nephrotic syndrome who are steroid toxic or poor response to Cyclophosphamide
- Severe aplastic anemia, pure red cell aplasia
- Recalcitrant psoriasis and atopic eczema

Reference ranges vary based on settings, indications and duration of transplant. Kindly discuss with physicians based on clinical judgement.

Assay used: Monoclonal Fluorescence Polarization Immunoassay

Recommended pre-dose Cyclosporine Concentration (C_0):

<table>
<tr><th>Indications</th><th>C_0 level (mcg/L)</th></tr>
<tr><td>Bone marrow transplant</td><td>Pediatric : 100 – 250 [6]
Adult : 250 – 500 [3]</td></tr>
<tr><td>Kidney transplant</td><td>Pediatric[6]
<3 months: 300 – 400
>3 months: 100 – 300

Adult – based on rejection risk [7]
<table>
<tr><th>Months</th><th>Low Risk</th><th>Moderate Risk</th><th>High Risk</th></tr>
<tr><td>0 – 6</td><td>150 – 275</td><td>175 – 325</td><td>200 – 350</td></tr>
<tr><td>7 – 12</td><td>100 – 200</td><td>125 – 225</td><td>150 – 250</td></tr>
<tr><td>>12</td><td>50 – 150</td><td>75 – 175</td><td>100 – 200</td></tr>
</table></td></tr>
</table>

Indications	C_0 level (mcg/L)
Liver transplant	Pediatric[6] <3 months: 200 – 250 >3 months: 100 – 125 Adult: 200 – 500 [3]
Others transplant (heart, lungs)	Pediatric: 100 – 400 [6] Adult: 300 – 500 [3]
Ulcerative colitis (Severe)	150 – 350 [4]
Aplastic anemia	75 – 200 [4]
Nephrotic syndrome	125 – 250[12]
Lupus nephritis	75 – 200[12]
Idiopathic thombocytic purpura	200 – 400[12]
Hypoplastic myelodyplastic syndrome	100 – 300[12]
Langerhans histocytosis	300 – 400[12]
Hemophagocytic lymphohistiocytosis	150 – 250[12]
Myasthenia gravis	300 – 500 [4]
Graft versus host disease	200 – 600 [4]

Recommended 2-hour (±15minutes) Post-dose Cyclosporine Concentration(C_2):

Indications	C_2 level (mcg/L)
Kidney transplant[7]	

Duration	C_2 level (mcg/L)
1 month	1700
2 months	1500
3 months	1300
4 – 6 months	900 – 1000
7 – 12 months	700 – 900
>12 months	700 – 800

Liver transplant[6]

Duration	C_2 level (mcg/L)
0 – 3months	1000
4 – 6months	800
> 6 months	600

DOSAGE:

Injection cyclosporine is in non-modified formulation (Sandimmune®). Oral cyclosporine is in modified formulation (Neoral®).

The IV dose is generally one-third the oral dose and should be adjusted based on clinical response, predefined blood concentrations, and tolerability. Because of the risk of anaphylaxis with the IV formulation, reserve IV administration for patients who are unable to tolerate oral cyclosporine formulations. [4]

Doses for obese patients should be based on ideal body weight.[5]

Pediatric:

Category	Dosage
Cardiac/ Liver/ Renal transplant rejection, in combination of Corticosteroid; treatment or prophylaxis [4]	6 months or older – refer to adult dose.
Graft versus host disease; prophylaxis[4]	*IV:* 1.5 mg/kg in 2 divided doses *PO:* 6.25mg in 2 divided doses
Nephrotic syndrome[8]	*PO:* 1 month – 18 years, 3 mg/kg BD, for maintenance reduce to lowest effective dose according to whole blood-cyclosporine concentrations, proteinuria and renal function
Psoriasis[1]	*PO:* 2.5 mg/kg/day in 2 divided doses may increase dose by 0.5 mg/kg/day if insufficient response is seen after 4 weeks. Maximum: 4 mg/kg/day
Rheumatoid arthritis[1]	*PO:* 2.5 mg/kg/day in 2 divided doses may be increased by 0.5 to 0.75 mg/kg/day if insufficient response is seen after 8 weeks of treatment. Maximum: 4 mg/kg/day

Adult:

Category	Dosage
Cardiac/ Liver/ Renal transplant rejection, in combination of Corticosteroid; treatment or prophylaxis[4]	*IV:* 5 to 6 mg/kg/day, with the first dose 4 to 12 hours before surgery and continue the initial daily dose postoperatively until the patient can tolerate oral administration. Alternatively, 1 mg/kg/day preoperatively, increased by 1 mg/kg/day every 24 hours until a maintenance dose of 4 mg/kg/day is reached. *PO:* 15 mg/kg to be given 4 to 12 hours before transplant or postoperatively, followed by 15 mg/kg/day given in 2 divided doses for 1 to 2 weeks period, titrated based on clinical response, predefined trough blood concentrations and tolerability.
Lung transplant rejection; prophylaxis[4]	*IV:* 2.4 mg/kg/day given as a continuous infusion over 24 hours. *PO:* 5 mg/kg/day in 2 divided doses
Graft versus host disease; prophylaxis[4]	*IV:* 3 to 5 mg/kg/day, usually administered as a continuous infusion beginning 1 or 2 days prior to transplantation. *PO:* 4 to 10 mg/kg/day
Aplastic anemia[4]	*PO:* 5 mg/kg/day in two divided doses
Psoriasis[4]	PO 2.5 mg/kg/day in 2 divided doses. After 4 weeks, the dose may be increased 0.5 mg/kg/day at 2-week intervals, depending on clinical response and tolerability. Maximum: 4 mg/kg/day.
Rheumatoid arthritis[4]	*PO:* 2.5 mg/kg/day in 2 divided doses, may be increased by 0.5 to 0.75 mg/kg/day after 8 weeks and again after 12 weeks, depending on clinical benefit and tolerability. Maximum: 4 mg/kg/day

Renal impairment:

Dosing alterations of cyclosporine during haemodialysis and peritoneal dialysis is not needed [4]

Category	Dosage
Cardiac/ Liver/ Renal Transplantation [4]	Reduce the dosage if nephrotoxicity develops
Psoriasis[1,4]	Decrease the dose by 25% to 50% for an elevation of serum creatinine of 25% or more above pre-treatment level on 2 tests 2 weeks apart or for any elevation of 50% or more above pre-treatment level. Discontinue treatment if reversibility of serum creatinine to within 25% of baseline is not attained after 2 dose reductions.
Rheumatoid Arthritis [4]	Decrease the dose by 25% to 50% for an elevation in serum creatinine of 30% above pre-treatment level. Discontinue treatment if the dose reduction does not control the abnormality or if the abnormality is severe.

Hepatic impairment:

It may require lower doses of modified cyclosporine for micro-emulsion to maintain blood concentrations within the recommended range. [4]

INTERACTION

Drugs that inhibit cytochrome P450 (CYP3A4) and P-glycoprotein (increase cyclosporine concentrations) [2]	Drugs that induce cytochrome P450 (CYP3A4) and P-glycoprotein (reduce cyclosporine concentrations) [2]
Calcium channel blockers	**Antibiotics**
Diltiazem	Rifampicin
Verapamil	Imipenem [1]
Antibiotics	**Antifungal**
Clarithromycin	Caspofungin
Erythromycin	Terbinafine [4]
Metronidazole	Griseofulvin [4]
HIV protease inhibitors	**Anticonvulsants**
Indinavir	Carbamazepine
Ritonavir	Phenobarbital
Gastrointestinal prokinetic agents	Phenytoin
Metoclopramide	**Others**
Immunosuppresants	Orlistat [3]
Sirolimus [1]	St. John's Wart
Tacrolimus [1]	Other CYP3A4 inducers
Antifungal agents	
Flucanazole	
Itraconazole	
Ketoconazole	
Voriconazole	
Others	
Bromocriptine	
Cimetidine	
Ethinyl estradiol	
Methylprednisolone	
Grapefruit juice	
NSAIDs	
Other CYP3A4 inhibitors	

SAMPLING

- Time to reach steady state: ~ 3 – 5 days
- Monitor every 4 to 7 days after conversion from non-modified to modified formulation.
- Monitor at least twice a week when converting patients to modified formulation at doses greater than 10 mg/kg/day, and daily if the initial dose exceeds 10 mg/kg/day, until the concentration is stabilized.[4]

Sampling time

- Most commonly utilized sample: Trough concentration[2]
- Concentration at 2 hours is a more sensitive predictor for acute rejection(especially during first year after transplantation).[2,9-11] There is a 15-minute period before and after the 2-hours time point, during which the C_2 sample can be taken to remain within an acceptable margin of error [2]

*Please use EDTA tube as whole blood need to be processed

MONITORING PARAMETER

- Monitor blood pressure and serum creatinine after any cyclosporine dosage changes or addition, modification or deletion of other medications. [1]
- Cyclosporine dosage should be decreased by 25% to 50% in patients with no history of hypertension who develop sustained hypertension during therapy and, if hypertension persists, treatment with cyclosporine should be discontinued.[1]

ADVERSE DRUG REACTION

Most of the adverse drug reactions resolved with dose reduction or discontinuation [3]

Adverse drug reaction (>10%):	
Cardiovascular	Hypertension, oedema
Central nervous system	Headache
Dermatologic	Hirsutism, hypertrichosis
Endocrine & metabolic	TG increased, female reproductive disorder
Gastrointestinal	Nausea, diarrhoea, gum hyperplasia, abdominal discomfort, dyspepsia
Neuromuscular & skeletal	Tremor, paresthesia, leg cramps
Renal	Renal dysfunction, creatinine increased
Respiratory	Upper respiratory infection
Miscellaneous	Infection

Overdosage/ Toxicology:

- Cyclosporine intoxication is an uncommon cause of poisoning. Ingestions are usually unintentional, and rarely result in severe manifestations.

- No antidote is available. Management of toxicity is mainly supportive. Activated charcoal may be given. Haemodialysis has no benefit. [4]

DILUTION AND ADMINISTRATION[1]

Oral [1]	May dilute oral solution with orange juice or apple juice. Avoid changing diluents frequently. Mix thoroughly and drink at once. Mix in a glass container and rinse container with more diluents to ensure total dose is taken. Do no administer liquid from plastic or Styrofoam cup.
Intravenous [1]	May administer by IV intermittent infusion or continuous infusion. For intermittent infusion, dilute 1ml (50 mg) of concentrated injection solution in 20 – 100 ml of D5W or NS, infuse over 2 – 6 hours. Discard diluted infusion solutions after 24 hours.

CALCULATION

A) Dose Initiation

1. Estimate clearance

$$\text{CL (L/hour)} = \text{CL (ml/kg/min)} \times \text{BW (kg)} \times 0.06$$

2. Determine the Css target and calculate the maintenance dose.

$$\text{MD(mg)} = \frac{\text{CL(L/hour)} \times \text{Css target (mcg/L)} \times \text{Interval (hour)}}{\text{S x F}} \times \frac{1}{1000}$$

3. Estimation of steady state concentration

$$\text{Css (mcg/L)} = \frac{\text{S X F X Dose(mcg)}}{\text{CL (L/hour)} \times \text{Interval (hour)}}$$

4. For calculation of intravenous dose (continuous infusion rate)

$$\text{ko} \left(\frac{\text{mcg}}{\text{hour}}\right) = \text{CL} \left(\frac{\text{L}}{\text{hour}}\right) \times \text{Css target(mcg/L)}$$

B) Dose Adjustment

1. Estimate CL from the obtained concentration

$$\text{CL (L/day)} = \frac{\text{S x F x Dose (mcg/day)}}{\text{Css (mcg/L)}}$$

2. Determine Css target and calculate the new maintenance dose

$$\text{MD (mg)} = \frac{\text{CL(L/hour)} \times \text{Css target (mcg/L)} \times \text{Interval (hour)}}{\text{S x F}} \times \frac{1}{1000}$$

Alternatively, assuming linear relationship between dose and concentration:

$$\text{Desired Dose(mg)} = \frac{\text{Css Desired}}{\text{Css Current}} \times \text{Current Dose (mg)}$$

CASE DISCUSSION

MCM is a 42-years-old, 75 kg male renal transplant patient who is receiving 75 mg twice daily of oral cyclosporine capsules. His steady state cyclosporine concentration has been below therapeutic range for the previous monitoring and the current concentration was 85 mcg/L. Upon assessment, the medication adherence was good with no missed dose since the last medication refilled. The patient stated that he has not been taking any new medications or traditional/complementary medicines since his post-transplant surgery. Based on rejection risk, the attending Nephrologist aimed for the concentration to be at least 100 mcg/L for optimal therapeutic outcome.

$$\text{Desired Dose(mg)} = \frac{\text{Css Desired}}{\text{Css Current}} \times \text{Current Dose (mg/day)}$$

$$\text{Desired Dose(mg)} = \frac{100}{85} \times 150$$

$$= 176 \text{ mg}$$

$$\sim 175 \text{ mg/day}$$

The new suggested dose is 75 mg in the morning, 100 mg in the evening. The Nephrologist planned to review the patient's cyclosporine concentration in 2 weeks for therapeutic confirmation.

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Clinical Pharmacokinetics Pharmacy Handbook
Second Edition

DIGOXIN

Digoxin is a cardiac glycosides known for its use in congestive heart failure and controlling ventricular response in atrial fibrillation and flutter. Historically, there were two cardiac glycosides used which are digitoxin and digoxin. However, digitoxin is no longer available since 1980s [18,21].

Digoxin exerts positive inotropic effects via inhibition of sodium-potassium ATPase pump, which affects the heart's contractility force. It also alters neurohormonal systems through autonomic nervous system effecting in digoxin's sinoatrial and atrioventricular nodal effects and an increase in baroreceptor sensitization [18].

Digoxin preparations available in Malaysia are in the forms of injection (250mcg/ml, 2ml ampoules), tablets (250mcg -white, round, biconvex tablets and 62.5mcg -blue, round, biconvex tablet) and elixir (50mcg/ml solution-clear, yellow, lime- flavoured) [13,16,17] .

KEY PARAMETERS:

Therapeutic Range	CHF: 0.5 – 0.9 mcg/L [1-4] AF: 0.8 – 2 mcg/L [4-7]
Bioavailability (F)	Tablets: 0.7 [4] IV and soft gelatine capsule: 1 [4] Elixir: 0.75 [16]
Salt Factor (S)	1 [4]
Volume of Distribution (Vd)	4 - 7 L/kg [8]
Clearance (CL)	0.57 – 0.86 ml/kg/min [4]
Half-life ($t_{1/2}$)	2 days [4]

PHARMACOKINETIC

Bioavailability (F):

The bioavailability of digoxin varies depending on dosage form.

Dosage form	Bioavailability
Intravascular Injection	100 % (1.0) [4,6,18]
Intramuscular Injection	Not recommended ~ 80% (0.8) [18]
Oral Capsules	90 – 100 % (0.95) [4,6,18]
Oral Tablets	63 – 75 % (0.7) [4,6,17,18]
Oral Elixir	75 – 80 % (0.75) [4,6,16,18]

Volume of Distribution (Vd):

- Digoxin distribution follows a two-compartment model [4] which digoxin initially distributes into a small initial Vd (plasma and other rapidly equilibrium organ) and then, further distributes into larger and more slowly equilibrium tissues (myocardium).

- The average volume of distribution is approximately ~7.3 L/kg and is influenced by disease and concomitant drugs used [8].

Age	Volume of distribution
Adults, normal renal function	6.7 ± 1.4 L/kg [6,8,18]
Adults, renal disease	4.8 ± 1.0 L/kg [6,8,18]
Children (1 – 12 years)	16. 1 ± 0.8 L/kg [18,19]
Infants	16.3 ± 2.1 L/kg [18]
Neonates, full term	10 ± 1 L/kg [18,19]

As digoxin does not distribute to adipose tissue, Vd in obese patient appears to be more closely related to the non-obese or Ideal Body Weight (IBW) [4].

$$\text{IBW for males (kg)} = 50 + 2.3\left(\frac{height\ (cm)}{2.54} - 60\right)$$

$$\text{IBW for females (kg)} = 45.5 + 2.3\left(\frac{height\ (cm)}{2.54} - 60\right)$$

Digoxin Vd is also decreased in hypothyroid patients and vice versa [4,6]. Hyperkalaemia and hyponatremia will decrease digoxin distribution to myocardium. In another word, hypokalaemia will increase digoxin distribution to myocardium [8].

Common factors that alter digoxin Vd:

- Quinidine: 0.7[9]
- Thyroid:
  - Hypothyroid: 0.7[4]
  - Hyperthyroid: 1.3[4]

* *Correction value(s) should be multiplied by calculated* $Vd_{digoxin}$.

Protein Binding: 20 - 30%, increased free fraction in uremic patients [9] and hypoalbuminemia (not clinically significant) [18].

Clearance (CL):

The metabolic clearance of digoxin is between 0.57 to 0.86 ml/kg/min and the renal clearance is approximately equal to CrCl. Digoxin clearance is also influenced by disease (CHF) and concomitant drugs used [6].

Common factors that alter Digoxin clearance:

- CHF: (refer formula) [4]
- Amiodarone: 0.5[4]
- Quinidine: 0.5[9]
- Verapamil: 0.75[4]
- Thyroid function
  - -Hypothyroid: 0.7[4]
  - -Hyperthyroid: 1.3[4]

**Correction value(s) should be multiplied by calculated* $CL_{digoxin}$ *in L/hr or L/day.*

Excretion of Digoxin [8,18]

- 50 – 70% of Digoxin is excreted unchanged by renal, primarily via glomerular filtration with some tubular secretion.
- 30 – 50% of Digoxin is excreted via non-renal, primarily through biliary and intestinal tracts.
- Small amount through metabolism (digoxin is a transport substrate for p-glycoprotein and concentrations are impacted by polymorphisms and drugs that may alter p-glycoprotein activity).

Half-life ($t_{½}$):

The half-life for digoxin depends on age and renal function [8].

Age	Half-life
Premature neonates	61 - 170 hours
Full-term neonates	35 - 45 hours
Infants	18 - 25 hours
Pediatric	35 hours
Adults	38 - 48 hours
Adults anephric	4 - 6 days

Indication and Therapeutic Range:

Positive inotropic effects of digoxin were seen with low digoxin concentration hence the lower therapeutic range is used in CHF. This lower target range is based on the fact that most patients with CHF do not demonstrate additional therapeutic benefits from higher digoxin concentration [1-2].

CHF: 0.5 – 0.9 mcg/L [1-4]

Since the goal for digoxin in AF is rate control, hence higher therapeutic concentration is needed [10].

AF: 0.8 – 2 mcg/L [4-7]

A serum concentration of ≥1.2 mcg/L may be associated with increased all-cause mortality in patients with atrial fibrillation (regardless of heart failure). Each increment of 0.5 mcg/L in serum digoxin concentration from the baseline concentration was associated with higher risk of death [22].

Digoxin maximum target concentration of 2 mcg/L was determined based on toxicity rather than efficacy. Heart rate at all levels of exercise in most patients with chronic AF is not adequately controlled by any therapeutic concentration of digoxin for which combination with other rate control agents should be considered [7,9].

DOSAGE

Pediatric: [19]

Age	Total digitalising dose (TDD[a,e]) (mcg/kg[b])			Daily maintenance dose[c] (mcg/kg[b])		
	Oral Solution	Tablets	IV/IM[d]	Oral Solution	Tablets	IV/IM[d]
Preterm neonates	20 – 30	-	15 – 25	5 – 7.5	-	4 – 6
Full-term neonates	25 – 35	-	20 – 30	8 – 10	-	5 – 8
1 – 24 months	36 – 60	-	30 – 50	10 – 15	-	7.5 – 12
2 – 5 years	30 – 45	-	25 – 35	8 – 10	-	6 – 9
5 – 10 years	20 – 35	20 – 45	15 – 30	5 – 10	6 – 11	4 – 8
>10 years	10 – 15	10 – 15	8 – 12	2.5 – 5	2.5 – 5	2 – 3

a. Initially give 50% of TDD, then give 25% of TDD in 2 subsequent doses at 6 to 8 hours interval. Obtained ECG 6 hours after each dose to assess potential toxicity. DO NOT give full TDD at once. Clinical response should be fully evaluated prior to additional doses (eg: ECG)
b. Based on lean body weight or IBW and normal renal function for age.
c. Given in two divided doses for neonates and pediatric less than 10 years old.
d. IM route is not recommended due to erratic absorption and severe pain at injection site [6].
e. Loading dose may not be necessary when treating heart failure.

Adult: [8,13,17]

Total digitalising dose (TDD[a,b]) (mg)		Daily maintenance dose (mg)	
Oral	IV/IM	Oral	IV/IM
0.75 – 1.5	0.5 – 1	0.125 – 0.5	0.1 – 0.4

a. Initially give 50% of TDD, then give 25% of TDD in 2 subsequent doses at 6 to 8 hours interval. Obtained ECG 6 hours after each dose to assess potential toxicity. DO NOT give full TDD at once. Clinical response should be fully evaluated prior to additional doses (eg: ECG)

b. Loading dose may not be necessary when treating heart failure.

Renal Impairment: [8,20]

Digoxin renal dose need not be adjusted for those with CrCl >50 ml/min. However, the dose should be reduced in patient with impaired renal function.

Renal dosage adjustment		
	CrCl	Dose
Loading dose	**10 – 50 ml/min**	No dosing adjustment required
	End Stage Renal Failure	Reduce 50% of TDD
Maintenance dose	**10 – 50 ml/min, CAV/VVHD**	25 - 75% of normal dose at normal interval OR administer normal dose every 36 hours. ~ 125 – 250 mcg per day, monitor serum concentration
	<10 ml/min, HD, HDF/High flux, Peritoneal dialysis	10 - 25% of normal dose at normal interval OR administer normal dose every 48 hours, ~ 62.5 mcg OD/EOD, monitor serum concentration ~ No supplemental dose needed after HD

- The amount of Digoxin dialyzed through HD is very small (~5%) and negligible.

INTERACTION

Increased drug concentration/effects:	Decreased drug concentration/effects:
Beta blocker – may have additive effects on heart rate [8]	Amiloride and Spironolactone – reduce the inotropic response to digoxin [8]
Inhibitors of P-glycoprotein efflux transporters: Amiodarone, Quinidine, Verapamil – reduce digoxin Cl [6,8,9,21]	Antacids (Mg/Al liquid), Cholestyramine and metoclopramide: reduce digoxin intestinal absorption [11,18,21]
ACE inhibitors – decrease renal Cl [18]	Levothyroxine and other thyroid hormone – increase Cl [8]
Tetracycline, Erythromycin, Clarithromycin – interfere with digoxin metabolism [18,21]	Inducers of P-glycoprotein efflux transporters: Rifampicin, Phenytoin – increase non-renal Cl [18,21]
Other CYP3A4 inhibitors– inhibits CYP3A4 which minimally metabolized digoxin [6,12]	Pregnancy – increase renal Cl and possible upregulation of p-glycoprotein [18]
	Hyperthyroidism- reduce myocardial responsiveness to digoxin, hypermetabolic and increased Cl [6]
Hypothyroidism- increase myocardial responsiveness to digoxin [18]	Bupropion – decrease digoxin concentration by 60% [21]

SAMPLING [4,8,19,21]

Time to monitor serum concentration:

When to obtain serum digoxin concentration (after dose initiation)	
With Loading dose	**12 – 24 hours** (at least 6 hours after last dose to ensure completion of distribution from the blood to the tissue)
Without Loading dose	**3 – 5 days**

When to obtain serum digoxin concentration (after dose adjustment)	
Maintenance dose	**Steady state:** **5 – 7 days after dose adjustment.** (continue to monitor digoxin concentration 7 – 14 days after dose adjustment) **Note**: In patient with end stage renal disease, it may take 15 – 20 days to reach steady state.
	Oral: 30 minutes prior OR just before next dose. If dose already taken wait at least 6 hours post dose.
	IV: 30 minutes prior OR just before next dose. If dose already taken wait at least 4 hours post dose.
**The sampling time for post dose (6 hours for oral and 4 hours for IV) is acceptable to avoid taking sample during the distribution phase.*	

Suspected toxicity:

- Blood can be withdrawn randomly (at any time).

Digoxin serum concentration should be monitored at steady state, unless these clinical condition occurs:

1. Questionable patient compliance
2. Evaluating clinical deterioration following an initial good response
3. Change in renal function
4. Suspected toxicity
5. Initiation or discontinuation of therapy with drugs which potentially interact with digoxin
6. Any disease changes

MONITORING PARAMETER

Symptomatic improvement: [6]	
Congestive Heart Failure	An improvement in common signs and symptoms of heart failure suggests therapeutic success. Common signs and symptoms of heart failure proposed by New York Heart Association (NYHA) [3]. a. Left-sided failure: dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, tachypnea, cough, haemoptysis, pulmonary oedema, S3 gallop, pleural effusion, Chyne-stokes respiration b. Right sided failure: abdominal pain, anorexia, nausea, bloating, constipation, ascites, peripheral oedema, jugular venous distention, hepatojugular reflux, hepatomegaly c. General symptoms: fatigue, weakness, nocturia, CNS symptoms, tachycardia, pallor, digital cyanosis, cardiomegaly.
Atrial Fibrillation	Heart/ ventricular rate (usually <100 beats/min) and electrocardiogram.
Possible interactions/toxicity potentiation:	
Electrolyte imbalance	Monitor for potassium level (hypokalaemia) especially if patient is on concomitant ACE inhibitor/diuretics). Monitor for hypomagnesaemia and hypercalcemia.
Renal function	a. Clinically unstable renal function: 2 – 3 times weekly monitoring. b. Stable renal function patient may only need monitoring of the serum creatinine when deem necessary.

ADVERSE DRUG REACTION

Researcher has found an increased incidence of adverse events when digoxin serum concentration exceeds >2 mcg/L:[6].

Adverse drug reactions: [6]	
Serum concentration >2.5 mcg/L	~50% will exhibit some form of toxicity involving: a. Gastrointestinal: anorexia, nausea, vomiting, diarrhoea, abdominal pain & constipation b. Central nervous system: headache, fatigue, insomnia, confusion, vertigo. Visual disturbances symptoms: blurred vision, change in colour vision, coloured halos around objects times involving the yellow-green spectrum. c. Cardiovascular: atrioventricular block/dissociation, bradycardia, premature ventricular contractions, ventricular tachycardia. New arrhythmia while receiving digoxin treatment shall be accounted for possible digoxin toxicity.
Other related ADR: [8]	
Dermatologic	Maculopapular rash; erythematous; scarlatiniform popular; vesicular or bullous rash; urticaria; pruritis; facial; angioneurotic or laryngeal oedema; shedding of fingernail or toenails; alopecia.
Neuromuscular & skeletal	Weakness.

Overdosage/Toxicology: [15]

Increased intracellular calcium leads to early depolarization, cardiac irritability, and dysrhythmias. Increased vagal and decreased sympathetic tones lead to bradycardia and heart block. Inhibition of the sodium-potassium ATPase pump causes hyperkalemia.

Patients with acute poisoning may develop severe bradycardia, heart block, vomiting, and shock. Hyperkalemia is a marker of severe acute toxicity and serum potassium level is the best predictor of cardiac glycoside toxicity after acute overdose. Severe chronic toxicity causes ventricular dysrhythmias and varying degrees of heart block.

Treat hyperkalemia if potassium concentration >5 mEq/L. Activated charcoal should be considered in all cases that present within 1 to 2 hours of ingestion as digoxin is well absorbed by charcoal. Haemodialysis does not increase the clearance of digoxin.

Antidote: Digoxin Immune Fab (DigiFab, Digibind)

- Mechanism of action: It binds to molecules of digoxin and form complex that will be excreted by the kidneys. As free serum digoxin is removed, tissue-bound digoxin is also released into the serum to maintain the equilibrium and is bound and removed by DigiFab. Thus, resulting in reduction in serum and tissue digoxin.

- This antidote is indicated in cases manifested by severe toxicity (ventricular dysrhythmias, progressive bradyarrythmias, 2nd or 3rd degree heart block), refractory hypotension, hyperkalemia (>5 mEq/L in acute overdose), significant risk of cardiac arrest (ingestion of >10 mg in adult, >4 mg in children, serum concentration >10 mcg/L 6 hours post ingestion), or lack of response to conventional therapy.

- Digoxin immune Fab preparation is available in the form of intravenous powder for solution of 40 mg. Each vial is mixed with 4 ml of sterile water for injection to yield 10 mg/ml. The reconstituted solution may be further diluted in normal saline to an appropriate volume for administration. For very small doses, the reconstituted solution can be diluted with 36 ml normal saline to achieve a concentration of 1 mg/ml [8,15]. Please refer to product inserts for complete administration instructions.

Digoxin Immune Fab Dosing	
Acute ingestion of unknown amount of digoxin	800 mg IV; ~start with 400 mg IV, observe response; repeat with remaining 400 mg IV as needed
Acute ingestion of known amount of digoxin	Dose of DigiFab (in vials) = $\frac{\text{digoxin ingested (mg) x bioavailability}}{\text{0.5 mg of digoxin bound per vial} *}$ *each vial of DigiFab 40 mg will bind 0.5 mg of digoxin
Chronic digoxin toxicity	240 mg IV OR Dose of DigiFab (in vials) = $\frac{\text{serum digoxin concentration (mcg/L) x weight (kg)}}{100}$

DILUTION AND ADMINISTRATION

Drug administration	
IV Bolus **Intermittent IV Infusion**	▪ May be infused undiluted. Administration rate > 5 minutes [13]. ▪ To be infused 10 – 20 minutes with max concentration 32 mcg/mL [13]. *IM route associated with muscle necrosis hence not recommended. If needed, not more than 500 mcg (adult) or 200 mcg (pediatrics) should be injected into a single site [13].
Dilution of drug	
	It can be given undiluted for IV bolus or diluted for IV infusion. a. Dilute in normal saline or dextrose 5% or water for injection [13-14]. b. Undiluted for IV bolus [8,13,14]. c. Further diluted the initial volume with >4 fold of compatible diluents as above, used less diluent may cause precipitation. *Diluted solution stable for 48 hours (room/fridge) [14]

CALCULATION

1. Dose Initiation

Maintenance dose: Oral/Intravenous

1. Estimate Clearance (CL):

a. Creatinine Clearance $\left(\frac{\text{mL}}{\text{min}}\right)$

$$= \frac{(140 - \text{Age})(\text{BW in kg})}{\text{Scr } (\mu\text{mol/L})} \times 1.23 \text{ (male) or } 1.04 \text{ (female)}$$

b. Digoxin Clearance (L/hr) =

- Patient without CHF = $[(0.8 \times \text{BW}) + \text{CrCL}] \times 0.06$

or

- Patient with CHF = $[(0.33 \times \text{BW}) + (0.9 \times \text{CrCL})] \times 0.06$

2. Determine Css target and calculate maintenance dose (MD):

$$\text{MD (mcg)} = \frac{\text{CL Dig (L/hr)} \times \text{Css target (mcg/L)} \times \text{Interval (hour)}}{\text{S} \times \text{F}}$$

Loading Dose

1. Estimate volume of distribution (Vd):

$$\text{Vd (L)} = (3.8 \times \text{BW}) + (3.1 \times \text{CrCL})$$

2. Determine Css target and calculate loading dose (LD):

$$\text{LD (mcg)} = \frac{\text{Vd(L)} \times \text{Css target (mcg/L)}}{\text{S} \times \text{F}}$$

2. Dose Adjustment

1. Estimate CL from the obtained concentration

$$\text{CL (L/day)} = \frac{\text{S} \times \text{F} \times \text{Dose (mcg/day)}}{\text{Css (mcg/L)}}$$

2. Determine Css target and calculate new maintenance dose

$$\text{MD (mcg)} = \frac{\text{Cl (L/day)} \times \text{Css target (mcg/L)} \times \text{Interval (day)}}{\text{S} \times \text{F}}$$

RESULT EVALUATION

CONCENTRATION	CONTRIBUTING FACTOR	RESPONSE	RECOMMENDATION
Subtherapeutic **< 0.5 mcg/L**	• **Compliance** • **Wrong sampling time** • **Insufficient dose** • **Drug Interaction** • **Disease Interaction**	**Poor** **Good**	**If compliance & sampling time is satisfactory, give incremental loading dose STAT (for patient in ward), then continue with current dose & resample** **Continue current dose**
Within normal therapeutic range 0.5 – 2.0 mcg/L		**Poor** **Good**	**Determine other factors that may contribute to poor response and treat accordingly** **Continue current dose**
Potential toxic/ Toxic **>2.0 mcg/L**	• **Overdosage** • **Underlying disease/ factors** • **Possible drug interaction** • **Renal failure** • **Hypokalemia** • **CHF**	**Toxic effect:** • **Vomiting** • **Hyperkalemia** • **Sinus bradycardia** • **Hyponatremia** • **Ventricular arrythmia** • **Weakness**	**Withhold treatment, monitor level and treat signs & symptoms of toxicity (if required), then adjust dose accordingly**

The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic – pharmacodynamic parameter and clinical condition should be considered before making any recommendations.

CASE DISCUSSION

Madam D, 60 years old, Malay lady, 60 kg, was admitted to Ward Mawar for management of community acquired pneumonia. She has underlying heart failure under the follow up at Cardiology Clinic. In ward, she developed fast atrial fibrillation with heart rate of 160 bpm. IV Digoxin 0.5 mg STAT was served to this patient. TDM was sent for this patient.

Lab Parameter (21.11.18)				
Urea: 3.1 mmol/L	***Na/K+ :135/ 3.2***	***Cr: 56 umol/L***		***HR: 100 bpm***
TDM Monitoring				
Drug Analysis	***Present Dose Regimen***	***Dose Started***		***Monitoring Date***
		Date	***Time***	***Random sample (Date/Time)***
IV Digoxin	0.5 mg STAT	21.11.18	0200H	21.11.18 1430H
Result: 0.76 mcg/L (Atrial Fibrillation: 0.8-2.0 mcg/L)				

1. Creatinine Clearance:

$$\text{CrCL(mL/min)} = \frac{(140-60)(60\text{ kg})}{56\ \mu\text{mol/L}} \times 1.04\ \text{(female)}$$

$$\text{CrCL} = 89.14\ \text{ml/min}$$

2. Estimate $CL_{digoxin}$:

   * Since patient has underlying HF, use

$$\text{Patient with CHF} = [(0.33 \times \text{BW}) + (0.9 \times \text{CrCL})] \times 0.06$$

$$CLdigoxin = [(0.33 \times 60\text{ kg}) + (0.9 \times 89.14\text{ml/min})] \times 0.06 = 6.00\ \text{L/hr}$$

3. Estimate volume of distribution (Vd):

$$\text{Vd (L)} = (3.8 \times \text{BW}) + (3.1 \times \text{CrCL})$$

$$\text{Vd (L)} = (3.8 \times 60\text{ kg}) + (3.1 \times 89.14\text{ ml/min}) = 504.33\text{ L}$$

4. a) Based on the current clinical condition, electrolyte and renal status of the patient, doctor planned to start patient with maintenance dose of Tab. Digoxin 0.125 mg OD.

Calculate the Css expected by using the following formula:

$$\text{MD (mcg)} = \frac{\text{CL Dig(L/hr)} \times \text{Css (mcg/L)} \times \text{Interval (hour)}}{\text{S} \times \text{F}}$$

$$\text{Css (mcg/L)} = \frac{\text{MD (mcg) x S} \times \text{F}}{\text{CL Dig}\left(\frac{\text{L}}{\text{hr}}\right) \times \text{Interval (hour)}}$$

$$\text{Css}\left(\frac{\text{mcg}}{\text{L}}\right) = \frac{125 \text{ mcg x } 1 \times 0.7}{6.00 \frac{\text{L}}{\text{hr}} \times 24 \text{ hr}} = 0.61 \text{ mcg/L}$$

To start with maintenance dose of Tab Digoxin 0.125 mg OD, as planned. To reassay a pre sample 5 days after starting the maintenance dose.

b) Based on the same situation as above scenario, doctor planned to serve another loading dose for this patient.

Calculate the incremental loading dose required for this patient by using the following formula:

$$\text{LD (mcg)} = \frac{\text{Vd(L)} \times [\text{Css target} - \text{C measured}\left(\frac{\text{mcg}}{\text{L}}\right)]}{\text{S} \times \text{F}}$$

$$\text{LD (mcg)} = \frac{504.33 \text{ L} \times [1.5 - 0.76 \text{ mcg/L}]}{1 \times 1} = 373.20 \text{ mcg}$$

As available preparation for Injection Digoxin is 250 mcg/ml, round off to the nearest dose ~ e.g. 250 mcg. So, calculate the Css expected for this dose:

$$250 \text{ mcg} = \frac{504.33 \text{ L} \times [\text{Css expected} - 0.76 \text{ mcg/L}]}{1 \times 1}$$

$$\text{Css expected} = 1.26 \text{ mcg/L}$$

Suggest to serve incremental loading dose of IV Digoxin 0.25 mg STAT. To reassay a random sample 12 hours after dose served.

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Clinical Pharmacokinetics Pharmacy Handbook
Second Edition

LITHIUM

Lithium, an effective mood stabilizer, is indicated for the treatment of bipolar disorder, especially for **acute mania and maintenance treatment of bipolar disorder.** Maintenance therapy reduces the frequency of manic episodes and diminishes the intensity of those episodes which may occur. In addition, lithium also appears to reduce the risk of suicide in patients with bipolar disorder.

KEY PARAMETERS:

Therapeutic Range	0.6-1.2 mmol/L
Bioavailability (F)	Capsule, immediate release tablet: 95-100% Extended release tablet: 60-90% Syrup: 100%
Volume of Distribution(Vd)	0.6-0.9 L/ kg
Metabolism	Not metabolized
Clearance(CL)	Normal lithium clearance varies between 10-40 ml/min, closely associated with CrCl, with the average of 20% CrCl.
Half-life($t_{1/2}$)	18-24 hours (can increase to >36 hours in elderly or with renal impairment)

PHARMACOKINETIC

Bioavailability (F):

Lithium is rapidly absorbed through the gastrointestinal tract; not affected by food.

Dosage forms	Time to peak concentration[1]	Bioavailability[1]
Lithium carbonate tablet/ capsule (rapid release)	1-3 hours	95-100%
Lithium carbonate tablet (sustained release)	4 – 8 hours	60-90%
Lithium citrate syrup	15 – 30 minutes	100%

Volume of Distribution (Vd):

Lithium is widely distributed throughout total body water with a volume of distribution at steady state ranging from 0.6 to 0.9 L/kg. However, the volume may be smaller in the elderly patients; less lean body mass and less total body water. Brain levels are highest within two hours of peak serum levels.

Metabolism and Clearance (Cl)

Lithium is not metabolized. It is excreted almost entirely by the kidneys as free ion.

Elimination	Extent of Elimination
Urine	Almost completely unchanged (>95%); 70-80% are reabsorbed
Saliva, Sweat, Feces	< 5%

It is not protein bound and a substantial amount of filtered lithium is reabsorbed ~ 70-80%; primarily in the proximal tubules. Therefore, renal lithium clearance is about 20% of creatinine clearance (CrCl). The half-life in adult patients with normal renal function is about 24 hours, and increases as renal function declines with age. Steady state is achieved within 4-5 days after the last dose change.

Categories [1]	V_d	t½ (hours)	Clearance (Cl)
Adult (normal renal function)	0.9 L/kg	24	20 ml/min
Pediatrics (9-12 years old)	0.9 L/kg	18	40 ml/min
Elderly (>65 years old)	NA	36	NA
Renal failure patients	NA	40-50	NA

Clearance in other special circumstances:

- ***Daytime*:** lithium clearance is increased by 30% due to the influence of circadian rhythm.
- ***Pregnancy***: clearance is increased during pregnancy especially on the 3rd trimester. Due to its possible teratogenic nature, use in 1st trimester is prohibited.
- ***Acute manic phase***: clearance increase as much as 50% (~ t½ will be half of the normal value).
- ***Sodium depletion condition (vomiting, diarrhea or excessive sweating) and/ or dehydration***: Sodium reabsorption is increased as a compensatory maneuver thus, lithium reabsorption also increases via the same pathway. Increased lithium reabsorption leads to decreased lithium clearance. Therefore, patients should be advised to maintain adequate fluid intake at all times (2.5-3 L/day) or to increase fluid intake as needed.

Indication and Therapeutic Range

Lithium is one of the effective mood stabilizer and is indicated for the treatment of bipolar disorder, especially for **acute mania and maintenance treatment of bipolar disorder.** However, it is the least effective for rapid cycling and mixed episodes of bipolar disorder. For mixed episodes, sodium valproate may be preferred over lithium.

Indication	Plasma trough concentration (mmol/L)
Acute mania	0.8 - 1.5
Maintenance dose	0.6 – 1.2

Elderly patients may require lower lithium concentration.

Lithium also has other indications in psychiatric conditions such as treatment of resistant depression, schizoaffective disorder and schizophrenia.

DOSAGE

Age	Dosage
Adult	Acute mania : 900-1200 mg/day (in 2-3 divided dose) Bipolar prophylaxis: 600 mg/day (in 2-3 divided dose)
Adolescent	600 -1800 mg/day (in 3 – 4 divided dose)
Children	15 – 60 mg/kg/day (in 3 – 4 divided dose)

Lithium doses can be slowly increased by 300 – 600 mg/day every 2-3 days according to clinical responses and lithium serum concentration. Since lithium follows first order linear kinetics, the steady state serum lithium concentration changes proportionally as the dose is changed.

Various prospective dosing methods exist in order to minimize the number of serum lithium concentration determinations and decrease the amount of time required to achieve a therapeutic dose such as Cooper method and Perry Method.

Example of Cooper method as follows:

Cooper Nomogram for Lithium Dosing [1] (Lithium Carbonate dosage required to produce steady-state lithium serum concentration between 0.6-1.2 mmol/L)

Lithium Serum Concentration 24H after the Test Dose (mmol/L)	Lithium Carbonate Dosage Requirement
<0.05	1200 mg three times daily (3600 mg/ day)
0.05 – 0.09	900 mg three times daily (2700 mg/ day)
0.10 – 0.14	600 mg three times daily (1800 mg/ day)
0.15 – 0.19	300 mg four times daily (1200 mg/ day)
0.20 – 0.23	300 mg three times daily (900 mg/ day)
0.24 – 0.30	300 mg twice daily (600 mg/ day)
>0.30	300 mg twice daily (600 mg/ day)

Dosage schedule determined to provide minimum fluctuation in lithium serum concentration and maximize patient compliance. A change in dosage interval can be made by the prescribing clinician, but the total daily dose should remain the same.

The Cooper Nomogram requires the administration of a single test dose of 600 mg lithium carbonate and a single lithium serum concentration measured 24 hours later. The 24-hours lithium serum concentration is compared to the above table that converts the observed concentration into the lithium carbonate dose that required to produce a steady state lithium concentration between 0.6-1.2 mmol/L. Perry Method also suggested similar concept but it employs a larger test dose of 1200 mg lithium carbonate.

Dosing: Renal impairment (adult) [10]

CrCl (mL/min)	Dose adjustment
10 – 50	50 – 75% of usual dose
<10	25 – 50% of usual dose

Dosing: Renal impairment (pediatric) [10]

CrCl (mL/min)	Dose adjustment
Immediate release (≥7 years and adolescents)	
30-89	Initiate therapy with low dose; titrate slowly with frequent monitoring
<30	Avoid use
Extended release (≥12 years and adolescents)	
>50	No dosage adjustment required
10-50	Administer 50-75% of normal dose
<10	Administer 25-50% of normal dose
ESRD with hemodialysis	Dose after dialysis

Dialysis [1,7-8]

Type of Dialysis	Lithium Clearance
Hemodialysis	50-90 ml/min
Peritoneal Dialysis	13-15 ml/min
Arteriovenous Hemodiafiltration	21 ml/min

INTERACTION

The concentration/effects of lithium may be increased by	The concentration/effects of lithium may be decreased by
Thiazide diuretics	Osmotic diuretics (mannitol)
*Angiotensin-Converting Enzymes Inhibitors (ACEi)/ Angiotensin Receptor Blockers (ARBs)	Methylxanthines (Theophylline, caffeine)
Non-Steroidal Anti-Inflammatory Drugs (except aspirin)	Carbonic anhydrase inhibitors (acetazolamide)
Spironolactone	
Calcium Channel Blockers (CCBs)	
Selective Serotonin Reuptake Inhibitors (SSRIs)- fluoxetine, sertraline, fluvoxamine	
**Frusemide	
**Amiloride	

**The onset of interaction with ACEi appears to be delayed (3-5 weeks) and elderly patients may be predisposed. It was reported that lithium serum concentration has increased by as much as 200-300% from pretreatment levels with ACEi.*

***Drugs that have minor, variable effects on serum lithium concentration. Because of this, many clinicians favour the use of loop diuretics, with careful monitoring of adverse effects and lithium serum concentration.*

Drug interaction between lithium and antipsychotic drugs also has been reported where patients are more susceptible to the development of extrapyrimidal symptoms (EPS) or neuroleptic malignant syndrome. Irreversible toxic encephalopathy has been reported with the use of high dose haloperidol, fluphenazine and flupenthixol. Thus, patients requiring co-treatment should be monitored for adverse drug reactions.

SAMPLING

Time to reach steady state:

4-5 days

Sampling time:

- Before the next morning dose or 12 hours from the last evening dose
- If based on initiation method (Cooper/ Perry method), lithium serum concentration is measured 24 hours after administration of a single test dose.

Frequency of sampling:

- *Patient with high risk of toxicity*: repeat lithium serum concentration every 2-3 days
- *Dose adjustment/ addition of drug with interaction*: measure within 1-2 weeks after changes
- *Acute mania patient*: re-measure once the manic episode is over and clearance returns to normal
- Once the desired steady-state lithium serum concentration has been achieved, lithium concentration should be rechecked every 1-2 weeks for approximately 2 months or until concentrations have stabilized. During maintenance therapy, lithium serum concentration should be repeated every 3-6 months and may be altered to every 6-12 months for patients whose mood is stable.

ADMINISTRATION

Oral: taken with food at the same time every day

MONITORING PARAMETERS

- Serum electrolytes
- BUN and serum creatinine (every 2 to 3 months during the first 6 months of therapy and every 6 to 12 months thereafter)
- Thyroid function test
- Complete blood count with differential
- Urinalysis (when output > 3L/day)
- Serum calcium (yearly)

ADVERSE DRUG REACTIONS

Common side effects:

Short term	Long term
Muscle weakness	Drug induced diabetes insipidus
Lethargy	Renal toxicity
Polydipsia	Hypothyroidism
Polyuria	ECG abnormalities
Nocturia	Leukocytosis
Headache	Dermatologic changes
Memory impairment	Weight gain
Confusion	
Hand tremor	
Fine motor performance impairment	

Toxicity [5]:

Severity	Serum concentration (mmol/L)	Symptoms
Mild	1.5 – 2.0	Vomiting, diarrhoea, ataxia, dizziness, slurred speech, nystagmus
Moderate	2.0 – 2.5	Nausea, vomiting, anorexia, blurred vision, chronic limb movements, convulsions, delirium, syncope
Severe	>2.5	Generalized convulsions, oliguria, renal failure

Management of toxicity:

Potential complications from lithium toxicity, including altered mental status and seizures, are treated with supportive care. Benzodiazepines are first line therapy for seizures.

- **Hydration**- Restoration of sodium and water balance in hypovolemic patients with lithium toxicity is essential to maximize lithium clearance

- **Gastrointestinal decontamination**- Gastric lavage may be attempted if the patient presents within one hour of ingestion. Whole bowel irrigation with polyethylene glycol (PEG) solution can be effective in patients with large acute ingestions or ingestions of sustained release preparations of lithium. There is no benefit from whole bowel irrigation in patients with chronic toxicity.

  Whole bowel irrigation should be given to awake asymptomatic patients who present within two to four hours after a presumed significant ingestion of sustained-release lithium (greater than 10 - 15 tablets). The dose is 500 mL - 2 L of PEG per hour via nasogastric tube until the rectal effluent is clear. Whole bowel irrigation is contraindicated in patients with altered mentation or lethargy.

- **Hemodialysis**[7]- Lithium is readily dialyzable due to its low molecular weight, negligible protein binding, and small volume of distribution. Therefore, hemodialysis is the treatment of choice for severe lithium toxicity. Treatment with hemodialysis for lithium toxicity may be considered in the following settings:

  - Serum lithium concentration is >5 mmol/L, or
  - Serum lithium concentration is >4 mmol/L and in patients with renal impairment (serum creatinine of >2.0 mg/dL or 150 mcmol/L), or
  - In the presence of decreased level of consciousness, seizure or life-threatening complications irrespective of the serum lithium concentration, or
  - Serum lithium concentration is >2.5 mmol/L and patient manifests signs of significant lithium toxicity (seizures, depressed mental status) has renal insufficiency or other conditions that limit lithium excretion or suffers from an illness that would be exacerbated by aggressive IV fluid hydration such as decompensated heart failure.

CALCULATION

1. DOSE INITIATION

Estimate Creatinine Clearance (CrCl):

$$\text{CrCl}\ (\frac{\text{ml}}{\text{min}}) = \frac{(140 - \text{Age})(\text{BW in kg})}{\text{Scr}\ (\mu\text{mol/L})} \times\ 1.23\ (\text{male})\ \text{or}\ 1.04\ (\text{female})$$

Estimate Clearance of Lithium:

CL (ml/min) = 0.2 [CrCl (ml/min)]
However, if convert to CL (L/d), the equation is as follow:

CL (L/d) = 0.288 [CrCl (ml/min)]

CL (L/d) = 0.432 [CrCl (ml/min)] - when acute mania

Determine the Css:

Css (mmol/L) = [F (D/τ)] /CL

F= 1 for oral lithium
D= dose, expressed in mmol unit; 300 mg of tablet lithium contains of 8.12 mmol Li^+ ion
T= dosage interval in days

2. DOSE ADJUSTMENT

D_{new} / $C_{ss,new}$ = D_{old} / $C_{ss,old}$

D_{new}= new daily dose

D_{old}= current daily dose

$C_{ss,new}$= new lithium serum concentration

$Cs_{s,old}$= current lithium serum concentration

CASE DISCUSSION

Case 1

AB is a 25 years old, 70 kg female patient (height= 165 cm, serum creatinine = 65 mcmol/L) who requires therapy with lithium. She is currently experiencing an episode of acute mania. Suggest an initial lithium carbonate dosage to achieve a steady state lithium concentration = 0.9 mmol/L.

Estimate creatinine clearance

This patient has a stable serum creatinine and is not obese. The equation below can be used to estimate creatinine clearance:

$$\text{CrCl}\left(\frac{\text{ml}}{\text{min}}\right) = \frac{(140 - \text{Age})(\text{BW in kg})}{\text{Scr }(\mu\text{mol/L})} \times 1.23 \text{ (male) or } 1.04 \text{ (female)}$$

CrCl = 128.8 ml/min

Estimate clearance

CL (L/d) = 0.432 (CrCl) - when acute mania

= 0.432 (128.8 ml/min)

= 55.64 L/d

Use average steady state concentration equation to compute lithium maintenance dose.

For a patient requiring therapy for acute mania phase of bipolar disease, the desired concentration is 0.8 – 1.0 mmol/L. A target serum concentration of 0.9 mmol/L was chosen and oral lithium carbonate will be used (F = 1, 8.12 mmol Li^+ /300 mg of lithium carbonate).

D/τ (mmol/d) = (Css x Cl)/ F

= (0.9 mmol/L x 55.64 L/d)/ 1

= 50.08 mmol/d

D/τ (mg/d) = (300 mg lithium carbonate/ 8.12 mmol Li^+)/ 50.08 mmol/d

= 1850.25 mg/d (rounded up to 1800 mg/d)

Thus, the dose required for AB is **1800 mg/day** which can be given as **600 mg TDS.**

Case 2

AB was prescribed with lithium carbonate 600 mg TDS. The measured lithium concentration is 0.6 mmol/L with frequent mood alterations. Compute a new oral lithium dose that will provide Css of 1.0 mmol/L.

Compute new dose to achieve desired serum concentration

D_{new} = $(C_{ss,new} / C_{ss,old})\ D_{old}$

= (1 mmol/L / 0.6 mmol/L) 1800 mg/d

= 3000 mg/d (rounded to 2700 mg/d)

AB will be prescribed a new dose of **900 mg TDS (2700 mg/day).** When the dose is altered, lithium concentration may be measured within 1-2 weeks after the change. During maintenance therapy, lithium serum concentration should be repeated every 3-6 months. This time period should be altered to every 6-12 months for patients whose mood is stable or every 1-2 months for patients with frequent mood changes.

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Clinical Pharmacokinetics Pharmacy Handbook
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METHOTREXATE

Methotrexate (MTX) is an antimetabolite that interferes with the metabolism of folic acid. After entry into the cell, methotrexate binds dihydrofolatereductase (DHFR) with an affinity greater than that of folate, and competitively inhibits conversion of dihydrofolate to tetrahydrofolate.

Tetrahydrofolate is essential for biosynthesis of thymidine and purines, which are important for synthesis of DNA. The blockade of tetrahydrofolate synthesis leads to inability of cell to divide and produce protein. Methotrexate is a part of therapy for acute lymphoblastic leukemia (ALL) and is active against in many types of cancer. High dose methotrexate (a dose higher than 500 mg/m^2) is used to treat a range of adult and childhood cancer [1].

Lower dose of MTX (15 mg to 25 mg weekly) is used to treat Rheumatoid Arthritis patient. It is often initiated as monotherapy. It can be also used with other disease modifying anti-rheumatic drugs (DMARDs) such as hydroxychloroquine and sulfasalazine. Absorption of oral methotrexate is generally via the protein coupled folate transporter in the small intestine and it is mainly renally excreted through glomerular filtration and active tubular secretion[2]. MTX is metabolized in the liver and about 10% of excretion is biliary with some enterohepatic recycling[3].Peak plasma concentrations occur at 1-2 hours after ingestion of low dose methotrexate and disappears from circulation at 24 hours [3].

KEY PARAMETERS:

Toxic Range	Variable; Refer to specific protocols. In general: Toxic if >0.1 µmol/L
Bioavailability (F)[10]	Parenteral: completely absorbed Oral: Low doses (<30 mg/m^2) - rapidly absorbed; Higher doses incompletely absorbed
Volume of Distribution (Vd)[9]	Initial Vd: 0.18 – 0.2 L/kg Steady state Vd: 0.4 – 0.8 L/kg Protein binding: 50 – 60%
Metabolism[12,13]	Minimally metabolized
Clearance (CL)[9]	Parent drug and metabolites: Renal Urine (48 – 100%); Biliary (<10%) $CL_{drug} \approx CrCl$ Estimated to be 1 – 2 times (≈1.65) the CrCl
Half-life ($t_{1/2}$)[14,15,16]	Biexponential: <u>Initial phase, α:</u> 1.5 – 3.5 hours (≈ 3 hours, when MTX concentration > 0.5 µmol/L) <u>Terminal, ß:</u> 8 – 15 hours (≈ 10 hours, become apparent when MTX concentration ≤0.5 µmol/L) Pediatric: 0.7 – 5.8 hours

PHARMACOKINETIC

Bioavailability (F): [10]

- Parenteral: Completely absorbed
- Oral : Low doses (<30 mg/m^2) - rapidly absorbed;
  Higher doses incompletely absorbed.

Volume of Distribution (Vd): [9]

- Initial Vd : 0.18 – 0.2 L/kg
- Steady state Vd : 0.4 – 0.8 L/kg
- Protein binding : 50 – 60%

Clearance (CL): [9]

- Parent drug and metabolites: via renal primarily
- Urine (48 – 100%); Biliary (<10%)

With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours.

$CL_{drug} \approx CrCl$, CL_{drug} is estimated to be 1-2 times (≈1.65) the CrCl.

Half Life ($t_{½}$):[14,15,16]

Biexponential:

- Initial phase, α:
  1.5 – 3.5 hours
  (≈3 hours, when MTX concentration >0.5 µmol/L)
- Terminal, ß:
  8 – 15 hours
  (≈10 hours, become apparent when MTX concentration ≤0.5 µmol/L)
- Pediatric: 0.7 – 5.8 hours

Indications: [4]

- Oncology-related uses:

Treatment of trophoblastic neoplasms (gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole), acute lymphocytic leukemia (ALL), meningeal leukemia, breast cancer, head and neck cancer (epidermoid), cutaneous T-Cell lymphoma (advanced mycosis fungoides), lung cancer (squamous cell and small cell), advanced non-Hodgkin's lymphomas (NHL), Osteosarcoma

- Non-oncology uses:

Treatment of psoriasis (severe, recalcitrant, disabling) and severe rheumatoid arthritis (RA), including polyarticular-course juvenile idiopathic arthritis (JIA)

DOSAGE

Refer specific protocols

(Pharmacist must identify the protocol used with prescriber before interpretation is done)

Summary of Protocols

Protocol	Dosage	Infusion Time	Leucovorin Rescue	MTX Concentration Time	Target (µmol/L)
ALL BFM SR/MR [22]	3 g/m^2	24 hours	Start 36 hours	48 hours	<0.25
ALL BFM Protocol M	3 g/m^2	24 hours	Start 36 hours	48 hours	<0.25
ALL BFM HR [22]	5 g/m^2	24 hours	Start 42 hours	48 hours	<0.1
Ph+ ALL [24]	5 g/m^2	24 hours	Start 42 hours	48 hours	<0.1

Relapsed ALL [19]	1 g/m^2	36 hours	Start 48 hours	60 hours	<0.1
Burkitt/NHL Group B [21]	3 g/m^2	3 hours	Start 24 hours (Complete 12 doses)	36 hours	<0.1
Burkitt/NHL Group C [21]	8 g/m^2	4 hours	Start 24 hours (Complete 12 doses)	36 hours	<0.1
Baby Brain Protocol [23]	3 g/m^2	24 hours	Start 36 hours	48 hours	<0.1
Osteosarcoma [18]	12 g/m^2 (max 20 g)	4 hours	Start 24 hours (Complete 7 doses)	24 hours	<0.1

Renal Impairment:[2,3,4]

- CrCl 61-80 ml/min : Decrease dose by 25%
- CrCl 51-60 ml/min : Decrease dose by 33%
- CrCl 10-50 ml/min : Decrease dose by 50% to 70%
- CrCl <10 ml/minute : Avoid use
- Hemodialysis : Not dialyzable (0-5%); supplemental dose is not necessary
- Peritoneal dialysis : Supplemental dose is not necessary
- CAVH effects : Unknown

Hepatic Impairment:

The FDA-approved labelling does not contain dosage adjustment guidelines

Chemotherapy protocols / Methotrexate Dosage / Leucovorin rescue dose

Leucovorin (a.k.a Folinic acid) is the rescue drug for Methotrexate toxicity if started early and guided by Methotrexate concentration, seems to be safe as the mainstay therapy.[7]

Leucovorin Protocol

Serum MTX Concentration (µmol/L)	<0.05	0.05 – 0.5	0.5 – 5.0	>5.0
Post 24 hours of Methotrexate infusion. To be measured 24 hourly till MTX concentration <0.05 µmol/L	No Leucovorin	10 mg/m² 6 hourly	100 mg/m² 6 hourly	1000 mg/m² 6 hourly

Generally, methotrexate concentrations <0.1 µmol/L is considered to be non-toxic for most of the cases. However, for certain patients or in certain centres, a non-toxic margin of methotrexate concentrations <0.05 µmol/L may be preferred.

Available Methotrexate Protocols

1. UMMC MA SPORE ALL 2003

2. ALL BFM 95 – SR / MR
   a. ACTUAL PROTOCOL
   b. ALL BFM 95 – PROTOCOL M
   c. PROTOCOL M (ANZCHOG ALL STUDY 8 – PILOT, PHASE III)
   d. ALL HR PROTOCOL (COG-AALL0232)

3. RELAPSED ALL (ALL-REZ BFM 2002 – PROTOCOL FOR TREATMENT OF CHILDREN WITH RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA)

4. OSTEOSARCOMA GUIDELINE (CHILDREN'S ONCOLOGY GROUP APPENDIX FOR AOST0331, PHASE III INTERROUP STUDY)

5. BABY BRAIN PROTOCOL (UKCCSH Infant Ependymoma Interim Guidelines)

6. BURKITT'S / NON-HODGKIN LYMPHOMA (UKCCSG, NHL GROUP; GUIDELINES FOR THE MANAGEMENT OF BURKITT/BURKITT LIKE AND B LARGE CELL NON-HODGKIN LYMPHOMA)

1. UMMC MA SPORE ALL 2003

MTX Dose	5 g/m^2 over 24 hours
MTX Concentration Monitoring	At 24 hours and then every 24 hours till Methorexate serum drug concentration <0.4 µmol/L

Leucovorin Dose

15 mg/m^2 every 6 hourly at 42 hours, 48 hours, 54 hours after start of IV Methorexate (3 doses)

2. ALL BFM 95 – SR / MR

a. ACTUAL PROTOCOL

- MTX concentration is taken at 24, 36, 42, 48, 54 and 72 hours from start of infusion
- If MTX concentration at 24 hours is NORMAL (<150 µmol/L) - start Leucovorin at 42 hours
- If MTX concentration at 24 hours is TOXIC (>150 µmol/L) – recheck concentration of methotrexate at 36 hours
- If MTX concentration at 48 hours is NORMAL (<3 µmol/L) - start Leucovorin at 42 hours
- If MTX concentration at 48 hours is TOXIC (>3 µmol/L) - start Leucovorin immediately

MTX concentration after starting MTX Infusion (µmol/L) At 24 hours	>150 µmol/L			>150 µmol/L		
	15 mg/m^2 every 6 hourly at 36 hours			15 mg/m^2 every 6 hourly at 42 hours, 48 hours, 54 hours		
MTX concentration after starting MTX Infusion (µmol/L) At 48 hours	>5	4.1 – 5	3.1 – 4	2.1 – 3	1.1 – 2	0.4 – 1
	>20 mg/kg over 1 hour	75 mg/m^2	60 mg/m^2	45 mg/m^2	30 mg/m^2	15 mg/m^2

b. ALL BFM 95 – PROTOCOL M

MTX Dose	Protocol M: 3 g/m^2 of MTX over 24hours [4 courses]
MTX Concentration Monitoring	At 48 hours and every 24 hours until MTX concentration <0.25 µmol/L
Leucovorin Dose	30 mg/m^2 stat at 36 hours after start of IV MTX then 15 mg/m^2 every 6 hourly for 7 doses.

c. PROTOCOL M (ANZCHOG ALL STUDY 8 – PILOT, PHASE III)

MTX Dose	Protocol M: 5 g/m^2 of MTX over 24 hours [4 courses]
MTX Concentration Monitoring	At 48 hours and every 24 hours until MTX concentration <0.25 µmol/L
Leucovorin Dose	30 mg/m^2 stat at 36 hours after start of IV MTX then 15 mg/m^2 every 6 hourly for 7 doses.

Leucovorin dose adjustment according Methotrexate concentration at 48 hours

MTX Concentration After starting MTX infusion at 48 hours	< 1µmol/L	1 – 5 µmol/L	>5 µmol/L
	15 mg/m^2 6 hourly	Increase dose according to treatment graph	May maximize dose to 100 mg/m^2 3 hourly

d. ALL HR PROTOCOL (COG-AALL0232)

MTX Dose	3 g/m^2 of MTX over 24hours [4 courses]
MTX Concentration Monitoring	At 48 hours. Targeted non-toxic MTX concentration <0.1 µmol/L
Leucovorin Dose	Start Leucovorin rescue at 42 hours from start of MTX

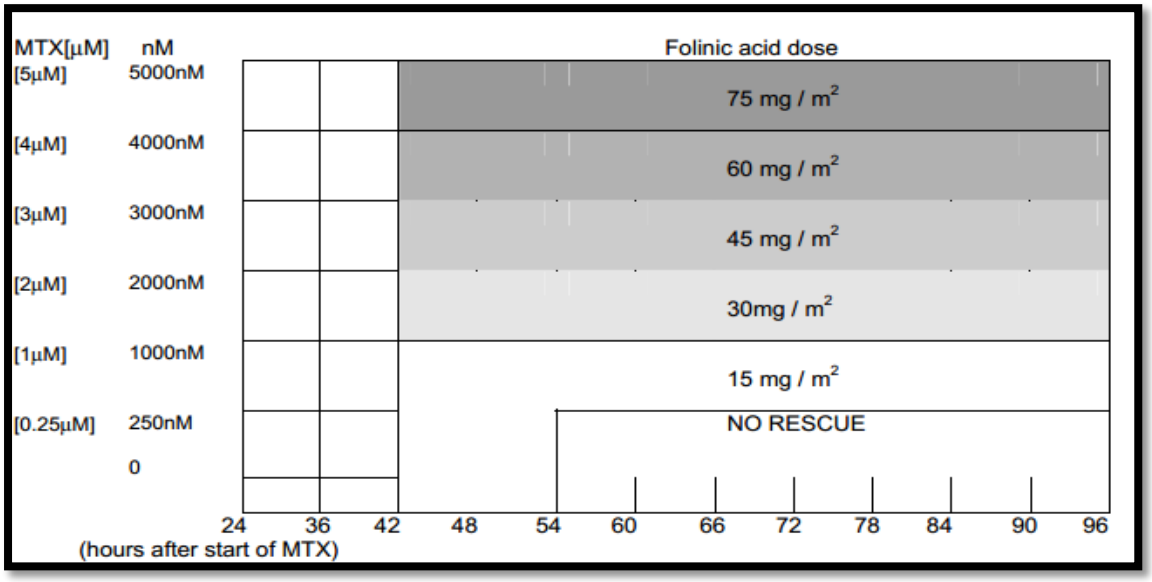

Figure 5.1 Diagram for calculating Folinic Acid Dose, based on MTX-Concentration (Calculated dose to be given at 6 hourly intervals)

3. RELAPSED ALL (ALL-REZ BFM 2002 – PROTOCOL FOR TREATMENT OF CHILDREN WITH RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA)

MTX Dose	• 1 g/m^2 over 36 hours [9 courses]
MTX Concentration Monitoring	• At 60 hours (before 3rd dose Leucovorin) • To adjust Leucovorin dose if high MTX concentration • Targeted non-toxic MTX concentration <0.1 µmol/L
Leucovorin Dose	• Start Leucovorin rescue at 48 hours from start of methotrexate

Hours after start of the MTX infusion	Expected MTX concentration (µmol/L)	Deviations of MTX concentration (µmol/L)
Post 36 hours	≤10.0	>10.0
Post 48 hours	≤0.5	>0.5

- Determine a methotrexate concentration every 6 hours (may include a concentration at 42 hours)
- Rescue IV Leucovorin every 6 hours until concentration ≤0.25 µmol/L
- Leucovorin dosed according to the diagram above (Figure 5.1) using the methotrexate concentration measured 6 hours earlier (if methotrexate at 42 hours >5.0 µmol/L, use the methotrexate concentration at 42 hours, however)
- To be started as soon as the methotrexate concentration at 48 hours (or 42 hours) is available

Hours after start of the MTX infusion	MTX concentration (µmol/L)	Management
Post 48 hours	>2.0 µmol/L	• Forced alkaline diuresis at 3 L/m^2
Post 48 hours	>5.0 µmol/L	• Carboxypeptidase • Forced alkaline diuresis at 4.5 L/m^2 • Leucovorin dose (mg) = weight (kg) x MTX concentration at 42 hours (µmol/L) • Additional Leucovorin doses are calculated based on the methotrexate concentration measured 6 hours earlier until this concentration falls below 5 µmol/L.

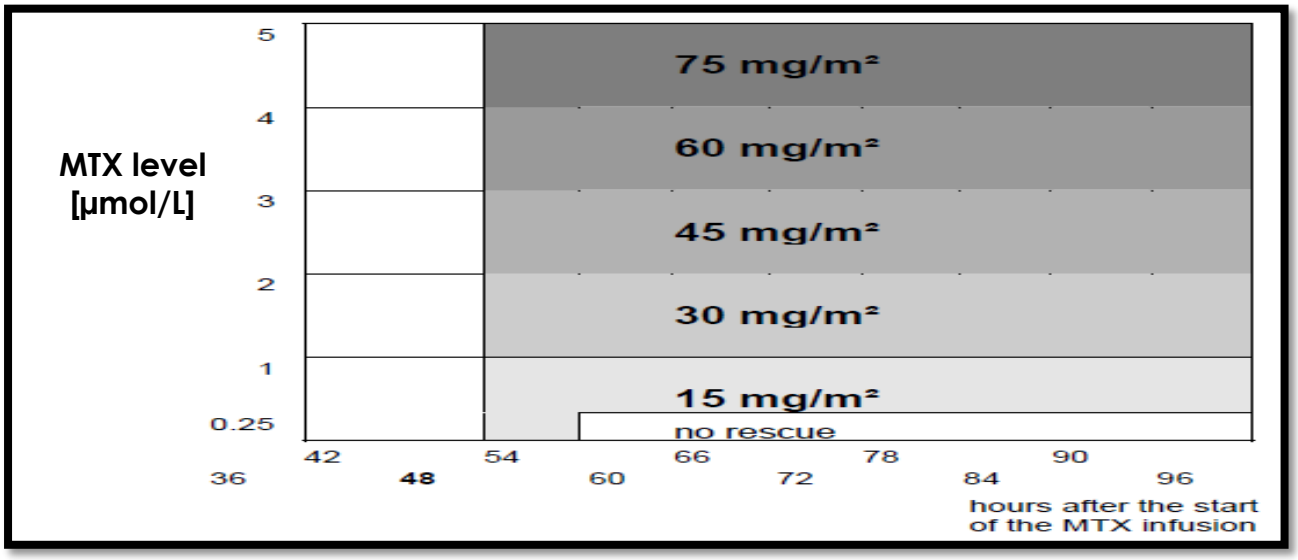

Figure 5.2 Leucovorin rescue for Methotrexate (1g/m^2/36h)

4. OSTEOSARCOMA GUIDELINE (CHILDREN'S ONCOLOGY GROUP APPENDIX FOR AOST0331, PHASE III INTERROUP STUDY)

MTX Dose	• 12 g/m^2 over 4 hours
	  ○ Pre-op 4 courses
	  ○ Post-op 8 courses

MTX Concentration Monitoring	• At 24 hours ○ Targeted non-toxic MTX concentration <0.1 µmol/L
Leucovorin Dose	• 10 mg/m^2 at 24 hours after start of IV MTX then 15 mg/m^2 every 6 hourly for total of 7 doses • Continue dose till MTX concentration <0.1 µmol/L, usually to complete all doses

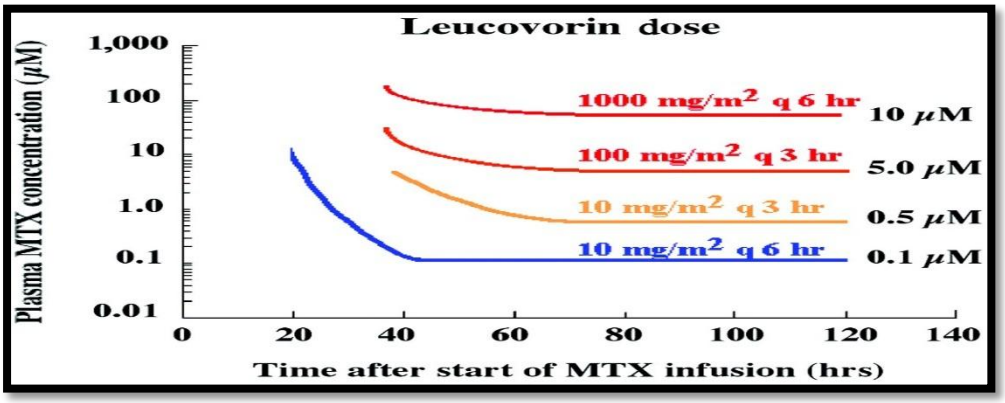

Figure 5.3 Leucovorin rescue for Methotrexate

5. BABY BRAIN PROTOCOL (UKCCSH Infant Ependymoma Interim Guidelines)

MTX Dose	• 3 g/m² as intravenous infusion ○ 10% dose over 1 hour, 90% dose over 23 hours, concurrent and post hyperhydration with $NaHCO_3$ • 100 mg/kg in pediatric <10 kg
MTX Concentration Monitoring	• At 24 hours ○ Non-toxic if concentration of methotrexate <0.1 µmol/L

Leucovorin Dose	• 15 mg/m² at 36 hours after start of IV methotrexate
	  ○ 15 mg/m² every 3 hourly for 5 doses then 6 hourly till concentration of methotrexate < 0.1 µmol/L at 48 hours
	  ○ Minimum 8 doses

Leucovorin rescue for Methotrexate (3g/m²/24h)

Time after starting MTX	Methotrexate plasma concentration (µmol/L)				
	<0.1	**0.1 – 2**	**2 – 20**	**20 – 100**	**>100**
48 hours	None[a]	15 mg/m² 6h	15 mg/m² 6h	10 mg/m² 3h	100 mg/m² 3h
72 hours	None	15 mg/m² 6h	10 mg/m² 3h	100 mg/m² 3h	1 gm/m² 3h
96 hours	None	15 mg/m²6h	10 mg/m² 3h	100 mg/m² 3h	1 gm/m² 3h
120 hours[b]	None	15 mg/m² 6h	10 mg/m² 3h	100 mg/m² 3h	1 gm/m² 3h

a. No extra Leucovorin is required provided methotrexate concentrations are below 0.1 µmol/L at 48 hours.

b. At time points after 120 hours Leucovorin administration should be continued as recommended for 120 hours.

6. BURKITT'S / NON-HODGKIN LYMPHOMA (UKCCSG, NHL GROUP; GUIDELINES FOR THE MANAGEMENT OF BURKITT/BURKITT LIKE AND B LARGE CELL NON-HODGKIN LYMPHOMA)

MTX Dose	• Group B – 4 courses of 3 g/m^2 of MTX over 3 hours • Group C – 4 courses of 8g/m^2 of MTX over 4 hours
MTX Concentration Monitoring	• MTX concentration at 36 hours (Before 3rd dose Leucovorin) • To adjust Leucovorin dose if high MTX concentration • Targeted non-toxic MTX concentration <0.1 µmol/L
Leucovorin Dose	• Start Leucovorin rescue at 24 hours from start of MTX • Total of 12 doses – to complete all doses or more

Leucovorin rescue for Methotrexate

Time after starting MTX	Methotrexate plasma concentration (µmol/L)				
	<0.1	**0.1 – 2**	**2 – 20**	**20 – 100**	**>100**
48 hours	None[a]	15mg/m^2 6h	15mg/m^2 6h	10 mg/m^2 3h	100mg/m^2 3h
72 hours	None	15mg/m^2 6h	10mg/m^2 3h	100mg/m^2 3h	1gm/m^2 3h
96 hours	None	15mg/m^2 6h	10mg/m^2 3h	100mg/m^2 3h	1gm/m^2 3h
120 hours [b]	None	15mg/m^2 6h	10mg/m^2 3h	100mg/m^2 3h	1gm/m^2 3h

a. No extra Leucovorin is required provided methotrexate concentrations are below 0.1 µmol/L (10^7 M) at 48 hours.

b. At time points after 120 hours Leucovorin administration should be continued as recommended for 120 hours.

INTERACTION[2,4]

Increase MTX concentration	Decrease MTX concentration
Ciprofloxacin Cyclosporine NSAIDs Penicillin Loop diuretics Proton pump inhibitors High dose salicylate	Bile acid sequestrants (decreased absorption of methotrexate)
Increased/enhances adverse/toxic effect of MTX	**Decrease MTX immunosuppressive effect**
Acitretin Trimethoprim Sulphonamide derivatives Doxycycline	N/A

SAMPLING[6,17]

Time to monitor serum concentration (at steady state)

- Usually measured at 24, 48, and 72 hours after starting the methotrexate infusion.
- Serum methotrexate concentration at 24, 42 & 48 hours must be determined immediately.
- Serum methotrexate concentration at 36 hours supposed to be optional.
- However, if serum MTX concentration at 24 hours is >150 µmol/L or/and suspicious of methotrexate overdose clinically (i.e significant increase in serum creatinine, decrease diuresis in spite of Frusemide), the serum methotrexate level at 36 hours must be determined immediately and to begin promptly at an increased value with the Leucovorin rescue as shown in the graph.
- It is advisable to start methotrexate infusion at 1400H in the respected institute so that the acceptance and measurement of the serum methotrexate concentration can be done within office hour.

MONITORING PARAMETER[4]

Patients with cancer [Baseline and frequently monitoring parameter (daily monitoring or every other day) during treatment]:

- Complete blood count with differential and platelets
- Renal profile
- Liver function tests
- Chest x-ray (baseline)
- Methotrexate concentrations
- Urine pH
- Pulmonary function test (if methotrexate-induced lung disease is suspected)

ADVERSE DRUG REACTION[4]

Adverse drug reactions (Concentration dependent toxicity)

- Delayed drug clearance is one of the major factors responsible for methotrexate toxicity.
- Toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to drug rather than peak level achieved.
- Renal dysfunction, third spacing (e.g. effusion) may delay methotrexate elimination causing methotrexate concentrations remain elevated for prolonged periods and this may increase toxicity.

PLASMA CONCENTRATION	SYMPTOMS
≥0.1 µmol/L for 48 hours or more	Myelosuppression (leukopenia, pancytopenia, thrombocytopenia, oral and gastrointestinal mucositis and acute hepatic dysfunction. Other clinical manifestations of toxicity include nausea, vomiting, diarrhoea, mucositis, stomatitis, esophagitis, elevated hepatic enzymes, renal failure, rash, myelosuppression acute lung injury, tachycardia, hypotension and neurologic dysfunction (depression, headache, seizures, motor dysfunction, stroke-like symptoms, encephalopathy, coma)

DILUTION AND ADMINISTRATION

Drug Dilution

Refer to specific protocols

Drug Administration [4]

In chemotherapy protocol, Methotrexate is usually administered as intravenous infusion (4 – 24 hours depending on specific protocols) and intrathecal.

General information

Therapeutic range

Acceptable Range (High dose methotrexate)

- MTX 24 HOURS : 5-10 µmol/L
- MTX 48 HOURS : 0.5-1 µmol/L
- MTX 72 HOURS : <0.1 µmol/L
- MTX RANDOM : <0.05 µmol/L (Undetectable)

LEUCOVORIN RESCUE PROTOCOL SUMMARY

Hours after start of MTX	MTX concentration (µmol/L)	Leucovorin dose(mg/m^2) QID
POST 24 HOURS	10.1-12	90
	12.1-18	150
	>18	300
POST 48 HOURS	1.1-1.8	15
	1.9-2.8	30
	2.9-8.5	90
	8.6-18	150
	>18	300

POST 72 HOURS	0.1-0.29	10
	0.3-1.8	15
	1.9-2.8	30
	2.9-9.8	90
	9.9-19	150
	>19	300
POST 96 HOURS	Refer concentration same as 72 hours Further serum MTX concentration may be done at daily	

Leucovorin dilution and administration

- Strength : 50mg/5ml
- Dilution: Dilute the required dose in 100ml-250 ml diluents
- Diluent : NS, D5, D10, NSD10, Ringers solution
- IV infusion: Administer over 15 minutes to 2 hours (NOT exceed 160 mg/min)

Stability after reconstitution:

Diluent	Room temperature (<25^{0}C)	Fridge (2^0-8^0)
Normal saline, Ringers	24 hours	-
D5, D10	12 hours	-
NSD10	6 hours	-

<u>Therapeutic range for oral Methotrexate</u>

- Rheumatoid arthritis : <0.1 µmol/L (Post 24 hours)
- Juvenile rheumatoid arthritis : >0.06 µmol/L (Post 1 hour)

  : <0.01 µmol/L (Post 24 hours)

CASE DISCUSSION

Case 1

Mr Z who is 42 years old Malay male was diagnosed with primary central nervous system lymphoma. His body weight was 80 kg and his height is 181 cm. Dr was prescribed IV Methotrexate 5015 mg STAT on 5 January 2019. Blood sample for therapeutic drug monitoring of Methotrexate is taken at Post 48 hours and Post 72 hours. The measured concentrations are as below:

- Post 48 hours: 1.23 µmol/L
- Post 72 hours: 0.42 µmol/L

Calculate body surface area (m^2)=

$$\sqrt{Height\ (cm) x\ Weight\ (kg)/3600}$$

$$= \sqrt{181\ cm\ x\ 80\ kg\ /3600}$$

$$= 2.0\ m^2$$

The measured post 72 hours MTX concentration is 0.42 µmol/L, which is <u>above</u> the therapeutic range. Based on Leucovorin rescue protocol, a dose of 15mg/m^2 leucovorin should be administered every 6 hours.

It is suggested to give IV Leucovorin 30 mg QID and resample a random MTX concentration after completed 24 hours leucovorin rescue therapy for therapeutic monitoring.

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Clinical Pharmacokinetics Pharmacy Handbook
Second Edition

PARACETAMOL

Paracetamol is commonly used for treatment of mild-to-moderate pain and fever (analgesic/antipyretic).

KEY PARAMETERS:

Bioavailability (F)	Oral: 85% to 98% [1]; rapidly absorbed in GI[1]
Volume of Distribution (Vd)	• Pediatrics, 0.7 – 1.2 L/kg[1] • Adults, 0.7 – 1 L/kg[1] • Protein Binding: 10% - 25%[1,2] 8% - 43% at toxic dose[2] • Crosses blood brain barrier[1] • May cross placenta[1]
Clearance (CL)	Total Body Clearance[1] • Pediatrics, 0.12 – 0.34 L/hr/kg • Adults, 0.27 L/hr/kg
Half-life ($t_{1/2}$)[1,2]	Neonate: 4 – 11 hours Pediatrics: 1.5 – 4.2 hours Adult: 2 – 3 hours (immediate release formulation) ~3 hours (extended-release formulation)
Therapeutic range	10-20 mg/L[3]

PHARMACOKINETIC

Metabolism:[1]

Paracetamol is metabolized mostly in the liver by conjugation with glucuronide, conjugation with sulphate and oxidation via the CYP isoenzyme system, mainly via CYP2E1.

The toxic reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI), is formed via the oxidative metabolism pathway and is conjugated with glutathione to form cysteine and mercapturic acid.

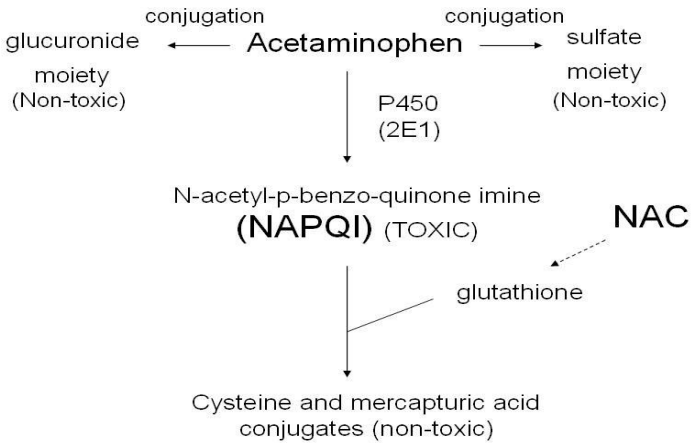


Figure 6.1 Paracetamol metabolism

(Adapted from Acetaminophen Toxicity, Medscape)

Metabolism of paracetamol may be slower but is similar in patients with liver impairment and in healthy subjects. Intra-patient environmental factors such as nutrition, alcohol use, smoking, etc., do not appear to significantly affect paracetamol metabolism.[1]

Indication and Toxic ranges: [3]

Minimum toxic doses of paracetamol for a single ingestion, posing significant risk of severe hepatotoxicity, are as follows:

- Pediatric: 150 mg/kg; 200 mg/kg in healthy pediatric aged 1 – 6 years[3]
- Adults: 7.5 – 10 g[3]

DOSAGE

Pediatric:

- **Oral:** 10 – 15 mg/kg/dose every 4 – 6 hours.[1,2] Maximum: 75 mg/kg/day (infants and children)[1] up to 4 g/day (children)[1]
- **Rectal: Infant and children ≤12 years, less than 60 kg** : 10 – 20 mg/kg/dose every 4 – 6 hours. Maximum: 5 doses (2.6 g) per day[1,2].

  Children ≥ 12 years and adolescent): 325 mg – 650 mg every 4 – 6 hours or 1000 mg 3 – 4 times daily. Maximum: 4 g/day.[1,2]

Adult:[1,2]

Oral: 650 mg – 1000 mg every 4 – 6 hours. Maximum: 4 g/day

Rectal: 325 mg – 650 mg every 4 – 6 hours or 1000 mg 3 – 4 times daily. Maximum: 4 g/day

Renal Impairment: [1]

A longer dosing interval and a reduced total daily dose of paracetamol may be warranted in cases of severe renal impairment (CrCl 30 ml/min or less).

It has been recommended to increase the dosing interval to every 8 hours in pediatric patients with severe renal failure (GFR less than 10 ml/min). No dose adjustments are required for pediatric patients with GFR 10 ml/min or greater.

Hepatic Impairment: [1]

Reduction of the total daily dose of paracetamol may be warranted when hepatic function is impaired. However, acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease.

INTERACTION[2]

Paracetamol may increase concentrations/ effects of :	Concentrations /effects of Paracetamol may be increased by:	Concentrations/effects of Paracetamol may be decreased by:
Aripiprazole Imatinib Vitamin K antagonist	Isoniazid Probenecid	Phenytoin Barbiturates Carbamazepine Cholestyramine resin Peginterferon Alfa-2b

Paracetamol increases the risk of liver damage in chronic alcoholics.

SAMPLING[4,5]

Sampling Time:

Acute overdosing:

- *1 – 8 hours after ingestion:* Sample at least 4 hours after ingestion
- *8 – 24 hours after ingestion*: Sample immediately on admission
- *> 24 hours after ingestion*: Sample immediately on admission
- *For unknown time of ingestion*: Sample immediately on admission

Repeated supra-therapeutic ingestion (chronic ingestion):

- Sample immediately on admission

MONITORING PARAMETER[3]

Most patients who have taken an overdose of paracetamol will initially be asymptomatic, as clinical evidence of end organ toxicity often does not manifest until 24 – 48 hours after an acute ingestion.

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels begin to rise within 24 hours after an acute ingestion and peak at about 72 hours. In severe overdose, transaminase elevation can be detected as early as 12 – 16 hours post-ingestion.

Toxicity is defined as serum AST or ALT levels greater than 1000 IU/L. A rapid progression of transaminase values to 3000 IU/L or higher reflects worsening hepatotoxicity.

Recommended chemistry tests are as follows:[3,4,6]

- Liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), bilirubin [total and fractionated], alkaline phosphatase)
- Prothrombin time (PT) with international normalized ratio (INR)
- Glucose
- Renal function studies (electrolytes, BUN, creatinine)
- Lipase and amylase (in patients with abdominal pain)
- Salicylate level (in patients with concern of co-ingestants)
- Arterial blood gas and ammonia (in clinically compromised patients)

Chronic ingestion or repeated supra-therapeutic dosing is generally defined as occurring over more than 4 – 8 hours.

In such cases, paracetamol concentration should be obtained along with liver function and coagulation profiles if the paracetamol concentration above 20 mg/L.

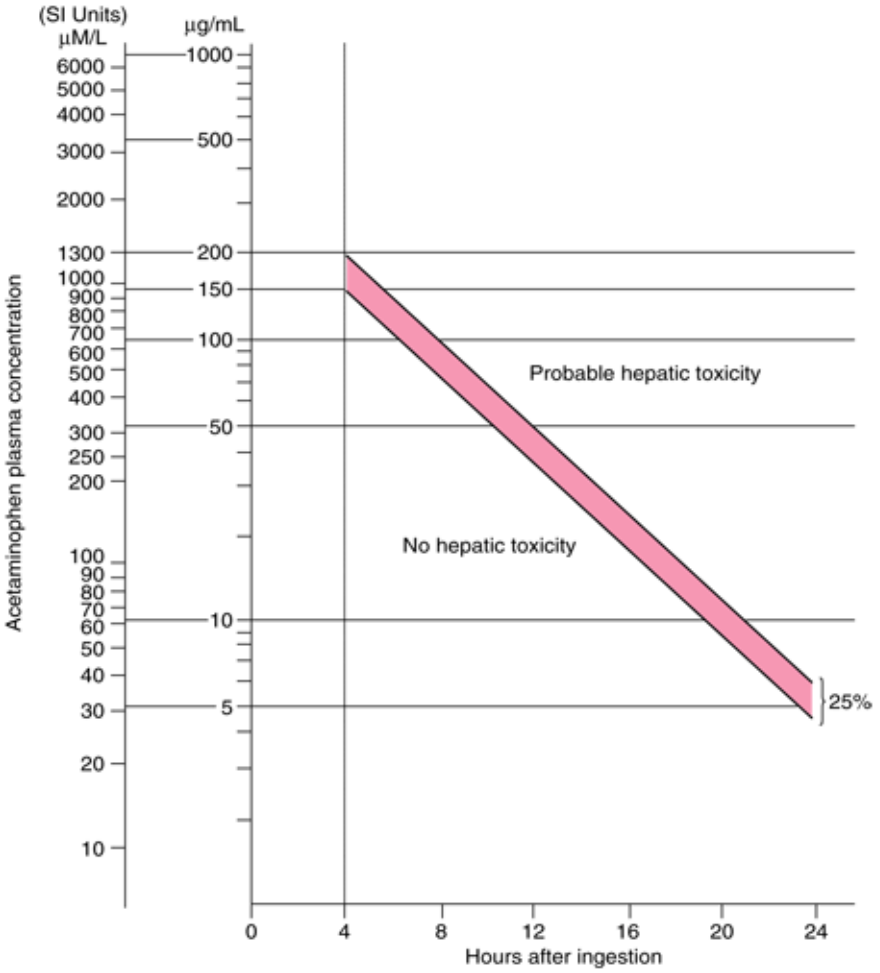


Figure 6.2 Rumack-Matthew Nomogram (Adapted from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity. Pediatrics 55(6): 871–876, 1975)

The Rumack-Matthew Nomogram predicts the risk of hepatotoxicity at a single concentration in time.[3] Nomogram tracking begins 4 hours after ingestion and ends 24 hours after ingestion.[3,6,9] Paracetamol plasma concentrations taken earlier than 4 hours may not be reliable. Concentrations obtained 4 – 18 hours post-ingestion are most reliable.[3]

The nomogram cannot be used if the patient presents more than 24 hours after ingestion or has a history of multiple paracetamol ingestions. Its reliability decreases for ingestions of extended-release paracetamol formulations.[3, 6]

If the paracetamol plasma concentration marked at the 'probable hepatic toxicity' line, it would be potentially hepatotoxic and requires antidote treatment. However, to provide safety buffer for patients who may have risk factors and a small margin of error against the estimation time of paracetamol ingestion, the 'treatment line' is plotted lower by 25% from the probable hepatic toxicity line .[7]

ADVERSE DRUG REACTION

The clinical course of paracetamol toxicity generally is divided into four phases. Physical findings vary, depending primarily on the level of hepatotoxicity.[3]

Phases of acute paracetamol poisoning.[3,6]

Phase	Duration	Description
Phase 1	0.5 – 24 hours after ingestion	• Patients may be asymptomatic or report anorexia, nausea or vomiting and malaise • Physical examination may reveal pallor, diaphoresis, malaise and fatigue
Phase 2	18 – 72 hours after ingestion	• Patients generally develop right upper quadrant abdominal pain, anorexia, nausea, and vomiting • Right upper quadrant tenderness may be present • Tachycardia and hypotension indicate ongoing volume losses • Some patients may report decreased urinary output (oliguria)
Phase 3: Hepatic phase	72 – 96 hours after ingestion	• Patients may have continued nausea and vomiting, abdominal pain, and a tender hepatic edge • Hepatic necrosis and dysfunction are associated with jaundice, coagulopathy, hypoglycaemia, and hepatic encephalopathy • Acute renal failure develops in some critically ill patients • Death from multi-organs failure may occur
Phase 4: Recovery phase	4 days to 3 weeks after ingestion	• Patients who survive critical illness in phase 3 have complete resolution of symptoms and complete resolution of organ failure

MANAGEMENT OF TOXICITY

For algorithm of paracetamol toxicity management, please refer appendix.

Activated Charcoal:

Activated charcoal may be given if paracetamol is likely to still remain in the GI tract.[6] Oral activated charcoal avidly adsorbs paracetamol and may be administered if the patient presents within 1 hour after ingesting a potentially toxic dose.[3,4]

N-Acetylcysteine (NAC):[3,6,7]

N-Acetylcysteine (NAC) is an antidote for paracetamol poisoning. This drug is a glutathione precursor that decreases paracetamol toxicity by increasing hepatic glutathione stores and possibly via other mechanisms. It helps prevent hepatic toxicity by inactivating the toxic paracetamol metabolite NAPQI before it can injure liver cells. However, it does not reverse damage to liver cells that have already occurred. Toxicity may still be reduced if it is started up to 24 hours after ingestion.

Delay in treatment with NAC can be associated with worse outcomes. Therefore treatment should be started immediately in children who present >8 hours after a significant ingestion or who are symptomatic of toxicity.

NAC Dose, Dilution and Administration

Intravenous NAC[1-6]

Three stage 20 hour infusion for patient <20 kg

1. 150 mg/kg NAC: diluted in 3 ml/kg 5% dextrose, infused over 60 minutes
2. 50 mg/kg NAC: diluted in 7 ml/kg 5% dextrose, infused over next 4 hours
3. 100 mg/kg NAC: diluted in 14 ml/kg 5% dextrose, infused over the next 16 hours

Three stage 20 hour infusion for patient 20 kg to 50 kg

1. 150 mg/kg NAC: diluted in 100 ml 5% dextrose, infused over 60 minutes
2. 50 mg/kg NAC: diluted in 250 ml 5% dextrose, infused over next 4 hours
3. 100 mg/kg NAC: diluted in 500 ml 5% dextrose, infused over the next 16 hours

Three stage 20 hour infusions for patient >50 kg

1. 150 mg/kg NAC: diluted in 200 ml 5% dextrose, infused over 60 minutes
2. 50 mg/kg NAC: diluted in 500 ml 5% dextrose, infused over next 4 hours
3. 100 mg/kg NAC: diluted in 1000 ml 5% dextrose, infused over the next 16 hours

Management for Acute Ingestion of Paracetamol[7]

Management of acute ingestion depends on time of paracetamol ingestion. For patient who are identified has been taken paracetamol within 1 hour; gastrointestinal decontamination with activated charcoal is recommended. However, study shows that efficacy of activated charcoal decreased beyond 60 minutes after toxic ingestion.

For patients who present within 1 to 8 hours from time of toxic ingestion, risk assessment is based on the serum paracetamol concentration plotted on the nomogram. Additional investigations such as liver function tests or a coagulation profile do not refine the risk assessment, and do not provide useful baseline data or change management in this group of patients. If serum paracetamol concentration shows "probable hepatic toxicity" on the nomogram, NAC should be administered within 8 hours from time of paracetamol ingestion.

In patients who present 8 hours or more after ingestion, evaluation of serum paracetamol concentration and ALT levels should be obtained as soon as possible. NAC should be initiated immediately if the reported dose exceeds the threshold for possible toxicity or the patient shows clinical signs suggestive of paracetamol toxicity; without waiting for the concentrations of serum paracetamol and ALT results. If the serum paracetamol concentration is subsequently found to be below the nomogram line, N-acetylcysteine may be stopped; if above the line, NAC treatment should be continued.

If the time of ingestion is unknown, it is safest to treat the patient as a delayed presentation. Thus, the recommendation is to follow the > 8 hours scenario. If there is a detectable serum paracetamol level (>20 mg/L) and the timing of ingestion cannot be accurately determined, NAC treatment should be initiated and serum ALT level measured.

Management for multiple or "staggered" Ingestion of Paracetamol[7]

If the patient has been ingested paracetamol less than 8 hours since the first dose; patient can be treated according to the 1–8 hours scenario. This is due to the paracetamol rapid absorption. Therefore, any subsequent doses will only lead to overestimation of the risk. Nevertheless, patient has been ingested paracetamol more than 8 hours since the first dose; treat the patient accordingly following the more than 8 hours scenario as in the Acute Ingestion Management Flow-Chart.

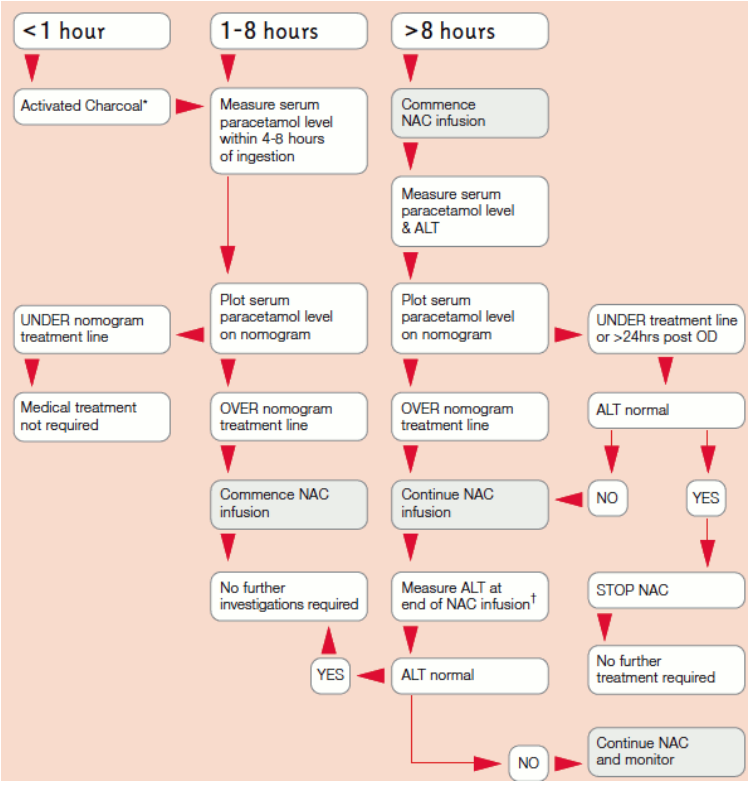


Figure 6.3 Algorithm for management of Acute Ingestion of Paracetamol[5]

Management for Overdose Ingestion of Sustained-Release Paracetamol[7]

If patient has ingested more than 200 mg/kg or 10 g (whichever is less), NAC treatment should be started immediately. However, if the amount ingested is less than 200 mg/kg or 10 g, the need for NAC can be determined by serum paracetamol concentrations.

In all cases, the serum paracetamol concentration should be taken at 4 hours or more post-ingestion and repeated 4 hours later. If the concentrations are above the nomogram line, NAC should be started or continued. However, if both levels fall under the nomogram line, NAC may be discontinued.

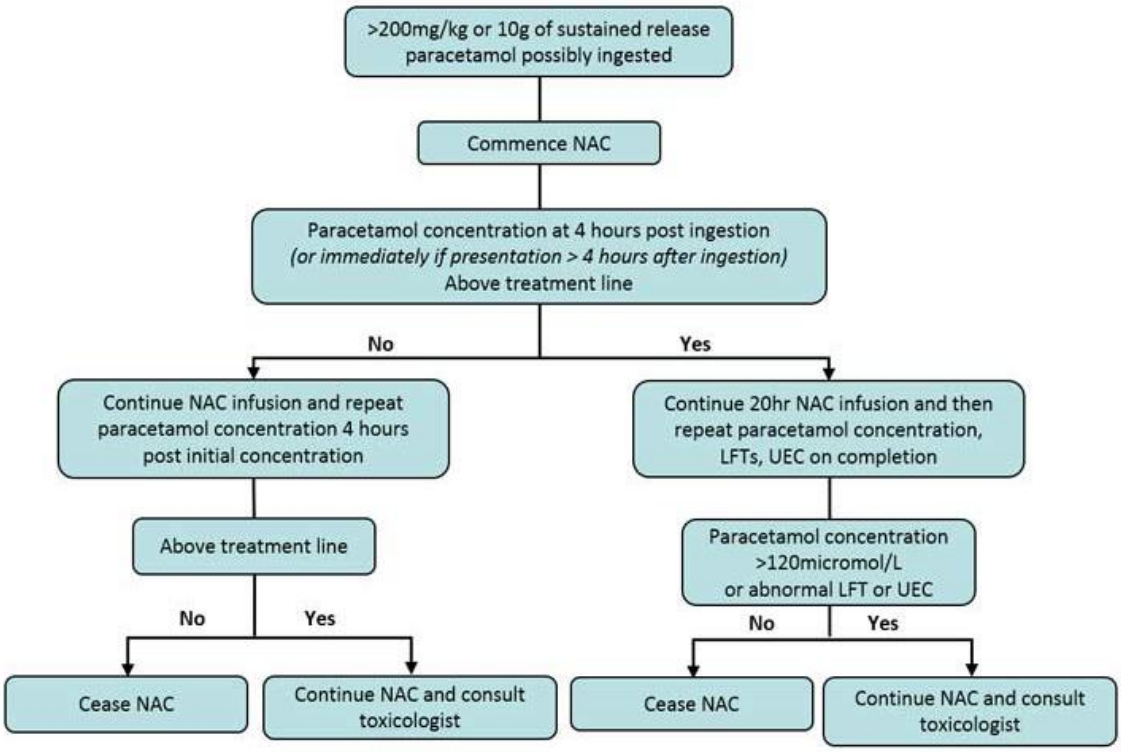


Figure 6.3 Algorithm for management of Overdose Ingestion of Sustained-Release Paracetamol[11]

CASE DISCUSSION

Patient SL, aged 18 years old with body weight of 52 kg presented with alleged paracetamol poisoning with suicidal intention on 9th February 2019 at 9.00 pm. Upon investigation with patient's family member, the attending Medical Officer was informed that 10 empty blister packs of 500 mg Paracetamol (100 tablets, 962 mg/kg) were found in patient's bedroom with patient lying on the bed, crying. Patient was then brought in to Emergency Department immediately by his family member. It was known that the patient is under Psychiatric Clinic follow up for depression.

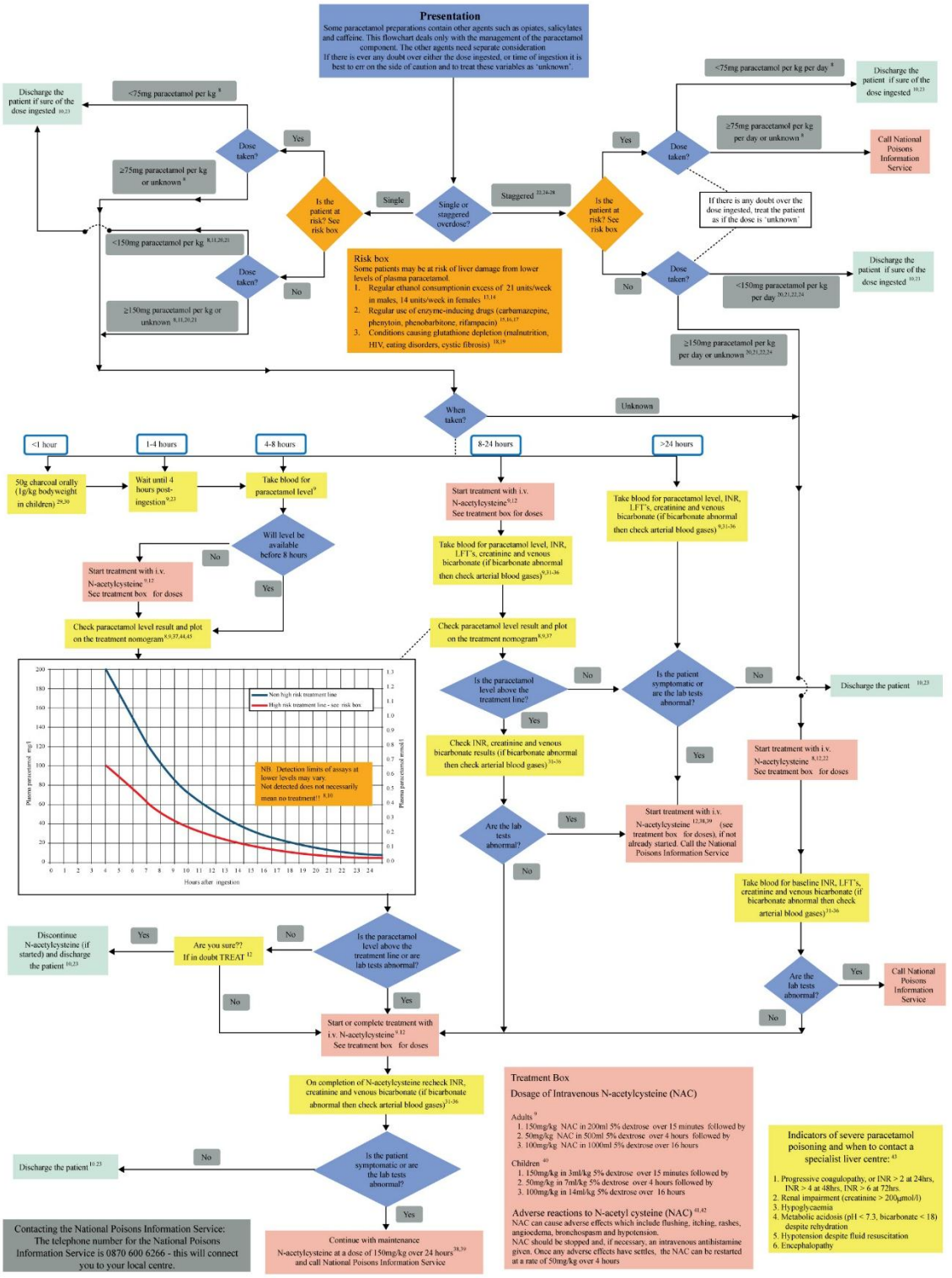
Upon arrival, blood for paracetamol analysis was sampled at 1am, 10th February 2019 (4 hours post ingestion) as requested by TDM pharmacist on-call. The measured level was 296.74 mg/L. Liver Function Tests (LFT) were also ordered and the finding revealed all liver enzymes were normal except for a raised in ALT with 120 U/L and total Bilirubin, 294 µmol/L.

Paracetamol level was plotted at 4 hours on Rumack-Matthew nomogram, which indicates any level of more than 200 mg/L is considered toxic. Thus, intravenous N-Acetylcysteine (NAC) was initiated following infusion protocol for body weight of >50 kg:

> 150 mg/kg NAC diluted in 200 ml 5% dextrose, infused over 60 minutes, then, 50 mg/kg NAC diluted in 500 ml 5% dextrose, infused over the next 4 hours and maintenance infusion of 100 mg/kg NAC diluted in 1000 ml 5% dextrose, over the next 16 hours. (Refer to subtopic G: Management of toxicity)

The patient was closely observed for the next 24 hours with repeated LFT showing ALT level has come down to 55 U/L and total Bilirubin of 103 µmol/L. All other investigations were within acceptable values and patient was clinically well. Upon discharge, patient was referred for mental health evaluation and the medical team planned for patient to continue his follow up under Psychiatric Clinic with an earlier appointment date.

Appendix: Algorithm for management of Paracetamol toxicity[4]



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Clinical Pharmacokinetics Pharmacy Handbook
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PHENOBARBITONE

Phenobarbitone is a long – acting barbiturate used in the treatment of seizure disorders, insomnia and anxiety. The principal central nervous system (CNS) – depressant action of phenobarbitone is related to increase in inhibitory neurotransmission via enhancement of gamma-aminobutyric acid-ergic (GABAergic) systems especially gamma-aminobutyric acid (GABA) receptor. Phenobarbitone is used as anticonvulsant for people with seizures disorders such as febrile seizures, tonic – clonic seizures, status epilepticus and eclampsia, although on rare occasions it is prescribed for daytime sedation. It is the first line treatment of neonatal seizures.

KEY PARAMETERS:

Therapeutic Range	15 – 40 mg/L [1]
Bioavailability (F)	Oral (capsules, tablets, elixir): 90 - 100% [1,2] Intravenous: 100% [1,2] Intramuscular: 100% [1,2] Rectal: 90% [1,2]
Salt Factor (S)	0.91 [1]
Volume of Distribution (Vd)	Neonate: 0.9 L/kg (0.7 – 1.0 L/kg)[1] Pediatric and adults: 0.7 L/kg (0.6 – 0.7 L/kg)[1]

Clearance (CL)	Pediatric: 0.008 L/kg/hr [1] Adults & neonates: 0.004 L/kg/hr [1] Elderly (>65 years old): 0.003 L/kg/hr [1]
Half life ($t_{1/2}$)	Neonates (<2 weeks): 111 ± 34 hours [2] Infants (2 weeks to <1 year): 63 ± 5 hours [2] Children (1 to <19 years): 69 ± 3 hours [2] Adults and geriatrics (>19 years): 96 ± 13 hours [2]
Steady State	Without LD: 2 - 4 weeks[2]

PHARMACOKINETIC

Bioavailability (F): [1,2]

Oral (capsules, tablets, elixir)	90 - 100%
Intravenous	100%
Intramuscular	100%
Rectal	90%

Volume Distribution (Vd): [1]

Neonate	0.9 L/kg (0.7 - 1.0)
Pediatric and adults	0.7 L/kg (0.6 - 0.7)

Protein Binding:

General	All population	47.8 %[4]
Specific	Neonate (<2 weeks)	37 ± 17 %[2]
	Infants and pediatric (2 weeks - 19 years)	51 %[2]
	Adult and geriatrics (>19 years)	51 %[2]

Clearance (CL):[1]

Pediatric	0.008 L/kg/hr
Adults & neonates	0.004 L/kg/hr
Elderly (>65 years old)	0.003 L/kg/hr

Half Life ($t_{1/2}$):[2]

Neonates (<2 weeks)	111 ± 34 hours [2]
Infants (2 weeks to <1 year)	63 ± 5 hours [2]
Children (1 to 19 years)	69 ± 3 hours [2]
Adults and geriatrics (>19 years)	96 ± 13 hours [2]

Conditions that might affect half-life of phenobarbitone: [2]

Cirrhosis	Increase
Pregnancy	Decrease
Prolonged starvation	Decrease
Renal failure (severe)	Increase
Hepato-renal	Increase

Indication and Therapeutic Range

General: 15 - 40 mg/L[1]

Clinical Condition [2]	Recommended Therapeutic Range [2]
Febrile convulsions	16 - 30 mg/L
Hypoxic ischemic seizures in neonates (perinatal asphyxia)	20 - 30 mg/L
Antenatal therapy to prevent intracranial haemorrhage in preterm infants	10 - 15 mg/L
Generalized tonic-clonic seizures	10 - 25 mg/L
Refractory status epilepticus	≥70 mg/L (up to 100 mg/L[10])
Cerebral salvage from hypoxic or traumatic brain damage	>75 mg/L

DOSAGE

Pediatric[6,8]

- **Loading dose in emergency:** Give 20 mg/kg IM or IV over 30 min STAT
- **Ventilated:** may repeat doses of 10 – 15 mg/kg, up to 120 mg/kg per day (beware of hypotension)
- **Usual maintenance:** 2 mg/kg (adult 100 mg) daily IV, IM or oral, increase to 3 – 8 mg/kg daily.
- **Sedation:** Oral: 2 mg/kg 3 times a day
- **Preoperative sedation:** Oral, I.M., I.V.: 1-3 mg/kg 1-1.5 hours before procedure

Adult[8]

- **Sedation:** Oral, IM: 30 – 120 mg/day in 2 – 3 divided doses
- **Preoperative sedation:** IM: 100 – 200 mg 1 – 1.5 hours before procedure
- **Anticonvulsant/Status Epilepticus:**
    - **Loading dose (IV):** 10 – 20 mg/kg (maximum rate ≤60 mg/minute in patient ≥60 kg); may repeat dose in 20 minute intervals as needed (maximum total dose: 30 mg/kg)
    - **Maintenance dose:**

      Oral, IV: 1 – 3 mg/kg/day in divided doses or 50 – 100 mg 2 – 3 times/day

Renal Impairment

CrCl <30 ml/min	Should be closely monitored[3]
CrCl <10ml/min	Administer every 12 – 16 hours[8]
Haemodialysis (moderately dialyzable: 20% to 50%)	Administer dose before dialysis and 50% of dose after dialysis[8]
Peritoneal dialysis	Administer 50% of normal dose[8]
CRRT	Administer normal dose and monitor concentrations[8]

- 20%-50% of phenobarbitone is excreted in urine unchanged. [11]
- Renal excretion is pH dependent with alkaline urine increasing renal clearance. [1]

Hepatic Impairment

- Phenobarbitone is 65 – 70% eliminated primarily by hepatic metabolism to inactive metabolites. [3]
- Dosing adjustment based on Child-Pugh Score[3]
- If score >8, decrease 25-50% of initial daily dose.[3]

INTERACTION[7]

The concentration/effects of Phenobarbital may be increased by[11]	The concentration/effects of Phenobarbital may be decreased by[11]
Carbonic Anhydrase inhibitor	Amphetamine
Chloramphenicol	Cholestyramine Resin
Clarithromycin	Folic Acid
Hydroxyzine	Ketorolac
Magnesium Sulphate	Leucovorin Calcium
Methylphenidate	Mefloquine
Phenytoin	Multivitamins/ Minerals
Primidone	Orlistat
Quinine	Pyridoxine
Valproic Acid and Derivative	Rifamycin derivative
	Tipranavir

SAMPLING

Time to monitor serum concentration (at steady state):

- Without loading dose: 2 - 4 weeks (after the initiation or a change in the regimen)[2]

Age[2]	Time to steady state (Days)
Neonates (<2 weeks)	16 - 30
Infant (2 weeks to 1 year)	12 - 14
Pediatric (1 to 19 years)	14 - 15
Adults and geriatric (>19 years)	17 - 23

Sampling Time:

- **Loading dose**

  2 -3 hours after administration[2]

- **Maintenance dose**

  Oral & IV: Just before next dose[1]

Sampling should be repeated when known enzyme inhibitors or inducers are added, adjusted or discontinued.[2]

More frequent monitoring may be required during pregnancy and for 8 weeks following delivery.[2]

MONITORING PARAMETER

- Phenobarbitone serum concentration [2]
- Concentration related side effect[2]
- Seizure activity (Fit Chart)[2]
- Liver function test[7]

ADVERSE DRUG REACTION [5]

Common	
• Ataxia • Dizziness • Drowsiness • Dysarthria • Fatigue • Headache • Irritability • Nystagmus	• Parethesia restlessness • Vertigo • Geriatric patient: Excitement, confusion, depression • Pediatric patient: Paradoxical excitement/hyperactivity
Less Common	
• Mental dullness • Constipation • Diarrhoea • Nausea	• Vomiting • Megaloblastic (folate-deficiency) anaemia
Uncommon	
• Rash • Hypocalcaemia	• Hepatotoxicity
Rare	
• Steven-Johnson syndrome • Rickets	• Osteomalacia

Concentration related side effect: [2]

Adverse Effect	Phenobarbital Concentration
Sedation	≥5 mg/L
Impaired cognition (with or without sedation)	>19 mg/L
Decreased neonatal feeding, respiration and muscle tone	>30 mg/L
Sedation, slowness, and ataxia	35 -80 mg/L
Potential coma	≥65 mg/L
Coma without reflexes	≥80 mg/L

Overdosage/Toxicology: [4]

Poisoning is uncommon but toxicity may be severe and may occur via oral or parenteral routes.

- **Mild To Moderate Toxicity**: Somnolence, slurred speech, nystagmus, confusion, and ataxia may occur.

- **Severe Toxicity**: Coma, hypotension, decreased myocardial contractility, hypothermia and respiratory failure. Concentrations of 60-80 mg/L are associated with coma and concentrations of 150-200 mg/L are associated with hypotension.

Management of Overdosage/Toxicology:

- Antidote: none
- Activated charcoal 0.25 to 0.5 g/kg may be given every 2 to 4 hours.
- Urinary alkalinisation can enhance the elimination of phenobarbital. Administer 1 to 2 mEq/kg (2 to 3 ampules of sodium bicarbonate mixed in 1L of D5W) given at 1.5 to 2 times maintenance fluid rates.
- Haemodialysis or haemoperfusion should be performed in patients who have haemodynamic instability not responding to supportive care or in patients who cannot tolerate a fluid load such as renal failure or congestive heart failure.

DILUTION AND ADMINISTRATION

Drug Dilution: [9]

Amount of Drug	Infusion Volume	Infusion time
<100 mg	50 ml	30 minutes
>100 mg	100 ml	30 minutes

Dilute in Normal Saline or Dextrose 5% (D5W) or Dextrose 10% (D10W) [7]

Drug Administration:

Intravenous

Avoid rapid administration of IV phenobarbitone. IV administration of >60 mg/minute in adults and >30 mg/minute in pediatric (may cause hypotension).[7,11]

Intramuscular

Inject deep into muscle. Do not exceed 5 ml per injection site due to potential for tissue irritation.[7,11]

Commercial injection is highly alkaline and can cause local tissue necrosis.[5]

CALCULATION

A) Dose Initiation

Maintenance Dose: Oral/Intravenous

1. Estimate Clearance
   - Pediatric: 0.008 L/kg/hr or 0.2 L/kg/day
   - Adult and neonates: 0.004 L/kg/hr or 0.1 L/kg/day

2. Determine Css target and calculate maintenance dose

$$\text{MD (mg)} = \frac{\text{CL(L/hour) x Css target (mg/L) x Interval(hour)}}{\text{S x F}}$$

Loading Dose: Intravenous

1. Estimate Volume distribution (Vd):
   - Neonates: 0.9 L/kg
   - Pediatric and Adult: 0.7 L/kg

2. Determine Css target and calculate loading dose (LD):

$$\text{LD (mg)} = \frac{\text{Vd(L) x Css target (mg/L)}}{\text{S x F}}$$

B) Dose Adjustment

1. Estimate CL from the obtained concentration

$$\text{CL (L/day)} = \frac{\text{S x F x Dose (mg/day)}}{\text{Css (mg/L)}}$$

$$\text{CL (L/hour)} = \frac{\text{CL (L/day)}}{24}$$

2. Determine Css target and calculate the new maintenance dose

$$\text{MD (mg)} = \frac{\text{CL (L/hour) x Css target (mg/L) x Interval (hour)}}{\text{S x F}}$$

RESULT EVALUATION

CONCENTRATION	CONTRIBUTING FACTOR	RESPONSE	RECOMMENDATION
Subtherapeutic <15 mg/L	• Compliance • Wrong sampling time • Insufficient dose • Drug interaction	Poor Good	If compliance and sampling time is satisfactory, increase the dose appropriately and resample Continue current dose
Within normal therapeutic range 15 - 40 mg/L		Poor Good	If compliance and sampling time is satisfactory, increase the dose (not more than the max recommended) Continue current dose
Potential toxic/Toxic >40 mg/L	• Overdosage • Underlying disease/factors • Possible drug interaction	Toxic effect: • Hypotension • Excessive sedation • Respiratory depression	Withhold treatment, monitor concentration and treat signs and symptoms of toxicity (if required), then adjust dose accordingly

The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic - pharmacodynamic parameter and clinical condition should be considered before making any recommendations.

CASE DISCUSSION

DD, a 26 years old, 65 kg male, is being treated with IV Phenytoin 1000 mg loading dose for status epilepticus but seizures were still uncontrolled. Phenobarbitone is to be initiated. Calculate a loading dose of Phenobarbitone that will produce a plasma concentration of 20 mg/L.

Step 1. Estimate volume of distribution (Vd):

Pediatric and Adult: 0.7 L/kg

Vd = 0.7 L/kg x 65 kg

= 45.5 L

Step 2. Determine Css target and calculate loading dose (LD):

$$LD\ (mg) = \frac{Vd\ (L) \times Css\ target\ (mg/L)}{S \times F}$$

$$LD\ (mg) = \frac{45.5\ L \times 20\ mg/L}{0.91 \times 1}$$

= 1000 mg

IV Phenobarbitone 1000 mg was initiated as loading dose, calculate an oral maintenance dose for DD which will maintain Phenobarbitone concentration of 20 mg/L. Also, how should the dose be administered?

Step 1. Estimate clearance

Adult and neonates: 0.004 L/kg/hr or 0.1 L/kg/day

CL (L/hr) = 0.004 L/kg/hr x 65kg

= 0.26 L/hr

Step 2. Determine Css target and calculate maintenance dose

$$\text{MD (mg)} = \frac{\text{CL (L/hr) x Css target (mg/L) x 12}}{\text{S x F}}$$

$$\text{MD (mg)} = \frac{\text{0.26 L/hr x 20 mg/L x 12}}{\text{0.91 x 1}}$$

= 68.57 mg 12 hourly

≈ 60 mg BD (available tablet strength = 30 mg per tab)

A month after the initiation of Tab Phenobarbitone 60 mg BD, the serum concentration obtained was 13 mg/L. What is your interpretation and recommendation?

Step 1. Estimate CL form the obtained serum concentration

$$\text{CL (L/day)} = \frac{\text{S x F x Dose (mg/day)}}{\text{Css (mg/L)}}$$

$$\text{CL (L/day)} = \frac{\text{0.9 x 1 x 120 mg/day}}{\text{13 mg/mL}}$$

CL (L/day) = 8.3 L/day

$$\text{CL (L/hour)} = \frac{\text{CL (L/day)}}{24}$$

$$\text{CL (L/hour)} = \frac{\text{8.3 L/day}}{24}$$

= 0.35 L/hour

Step 2. Determine Css target and calculate the new maintenance dose

$$\text{MD (mg)} = \frac{\text{CL (L/hour) x Css target(mg/L) x Interval (hour)}}{\text{S x F}}$$

$$\text{MD (mg)} = \frac{\text{0.35 L/hour x 20 mg/L x 12 hours}}{\text{0.91 x 1}}$$

= 92.3 mg BD

≈ 90 mg BD

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PHENYTOIN

Phenytoin is an antiepileptic drug that can be used in the treatment of epilepsy. Phenytoin is a narrow therapeutic window drug, highly protein bound and has a nonlinear pharmacokinetics. The primary site action of Phenytoin is at the motor cortex where the spreading of seizure activity is inhibited. Phenytoin tends to stabilize the threshold against hyper-excitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient possibly by promoting sodium efflux from the neurons. It includes the decreasing of post tetanic potentiation at synapses and the loss of post tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin will reduce the maximal activity of brain stem centres that responsible for the tonic phase of tonic-clonic (grand mal) seizures. Phenytoin is used for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures. It's also used as a prevention and treatment of seizures occurring during or following neurosurgery.[9]

KEY PARAMETERS:

Therapeutic Range	10 – 20 mg/L	
Bioavailability (F)	1	
Salt Factor (S)	1	
Volume of Distribution (Vd)	0.6 – 0.7 L/kg	
Clearance (CL)	**Vm**	**Km**
	8.45 mg/kg/day[6]	6.72 mg/L [6]
	7 mg/kg/day[1]	4 mg/L [1]
Half-life ($t_{1/2}$)	Concentration dependant	

PHARMACOKINETIC

Bioavailability (F):[1]

	IV	Capsule	Susp/Chew Tab
Bioavailability, F	1	1	1
Salt Factor, S	0.92	0.92	1

Time to steady state:

No loading dose	7 - 10 days [10]
With loading dose	24 hours[1]

Volume of Distribution (Vd):[1,2]

Neonates	1 – 1.2 L/kg (premature)
	0.8 – 0.9 L/kg (term)
Infants	0.7 – 0.8 L/kg
Pediatric	0.7 L/kg
Adult	0.65 - 0.7 L/kg

Half life ($t_{½}$):[1,2]

Oral: 22 hours (range 7 – 42 hours)

IV: 10-15 hours[10]

Protein binding: [1,2]

Neonates	≥ 80% (≤ 20% free)
Infants	≥ 85% (≤ 15% free)
Adult	90 – 95 %

Metabolism:[3]

- Hepatic
- Dose dependent capacity (Michaelis-Menten pharmacokinetics)

Elimination:[3]

- Urine

Clearance:

	Vm	Km
Adult	8.45 mg/kg/day[6]	6.72 mg/L[6]
	7 mg/kg/day[1]	4 mg/L[1]
Infant	10 –14 mg/kg/day[1]	6 mg/L[1]

[6] Data by local population

Indication and Therapeutic Range:[4]

Clinical Condition	Recommended Therapeutic Range
Status Epilepticus / Anticonvulsant	10 – 20 mg/L

DOSAGE

Pediatric: [4]

Status Epilepticus	**LD**	IV: 15 – 20 mg/kg over 1 hour
	MD	5 mg/kg/day in 2 divided doses
Anticonvulsant	**LD**	Oral: 15 – 20 mg/kg in 3 divided doses every 2 – 4 hours
	IMD	5 mg/kg/day in 2-3 divided doses
	MD	4 – 8 mg/kg/day (maximum daily doses: 300 mg)

Adult:[4]

Status Epilepticus	**LD**	IV: 10 – 20 mg/kg (at a rate not exceeding 50 mg/min) followed by maintenance doses of 100 mg orally or IV every 6-8 hours.[10]
	MD	IV or oral: 100 mg every 6 – 8 hours
Anticonvulsant	**LD**	Oral: 15 – 20 mg/kg in 3 divided dose every 2 – 4 hours
	IMD*	300 mg in 3 divided doses
	MD	300 – 600 mg daily

**Initial maintenance dose*

Renal Impairment: [4]

Phenytoin serum concentration in renal impairment patient might be difficult to interpret directly from the result due to the present of hypoalbuminemia and renal impairment itself. Because of that, some adjustments may need to be done to allow accurate interpretation. If possible, it is ideal to obtain free phenytoin plasma concentration (unbound fraction).

Hepatic Impairment: [4]

The used of phenytoin in mild to moderate hepatic impairment is generally safe. The clearance of phenytoin may be substantially reduced in cirrhosis. Monitoring phenytoin concentration with possible dose adjustment may be needed in certain patient and generally advisable. Free phenytoin concentration may be needed if available.

INTERACTION

The concentration/effects of phenytoin may be increased by [4]	The concentration /effects of phenytoin may be decreased by [4]
Allopurinol	Carbamazepine
Amiodarone	Ciprofloxacin
Azole derivatives	Folic Acid
Calcium Channel Blocker	Methotrexate
Carbamazepine	Pyridoxine
Cefazolin	Rifampin
Chloramphenicol	Ritonavir
Fluoxetine	Theophylline
Fluvoxamine	Valproic Acid
Hydroxyzine	
Isoniazid	
Proton Pump Inhibitors	
Serotonin Reuptake Inhibitors	
Sulfonamide Derivatives	
Tacrolimus	
Ticlopidine	
Topiramate	
Trimethoprim	
Vitamin K Antagonist	

SAMPLING

Time to monitor serum concentration (at steady state): [1]

After LD: [8]

- 2 hours after completion of IV loading dose (if rapid therapeutic concentration is needed)
- 24 hours after administration of an oral loading dose

Without LD:

- 7 – 10 days (after the initiation or a change in the regimen) [10]

Sampling Time:

Loading dose: [8]

First concentration:

- Oral: 24 hours after administration of oral loading dose
- IV: 2 hours after completion of IV loading dose to aid in determining maintenance dose or need to reload.

Maintenance dose

- IV/Oral: Just before next dose [1]

MONITORING PARAMETER[4]

- Complete Blood Count
- Liver Function (Albumin level)
- Renal Profile (Serum Creatinine)
- Suicidality (suicidal thoughts, depression, behavioural changes)
- Fit Chart
- Blood Pressure, Vital Signs (with IV use)

ADVERSE DRUG REACTION

Dose related side effects:[4]

- Far lateral nystagmus (>20 mg/L)
- Ataxia (>30 mg/L)
- Diminished mental capacity (>40 mg/L)

Gingival hyperplasia, hirsutism, coarsening of facial features, and peripheral neuropathy are not dose related side effects and is not an indication for TDM in patients receiving Phenytoin.

Overdosage/Toxicology:[7]

There are thousands of exposures reported to poison centres every year, as Phenytoin is a widely used anticonvulsant. However, deaths are extremely rare and severe manifestations occur in only a minority of cases.

Management of Overdosage/Toxicology:

- Treatment is supportive.
- Activated charcoal could be considered if the patient is awake, alert, and cooperative, and the ingestion is relatively recent (within the last hour). Gastric lavage should be avoided in most phenytoin overdoses as it is not life-threatening.
- No indication for haemodialysis, haemoperfusion, or urinary alkalinisation.
- Monitor phenytoin concentrations every 4 hours until the concentrations are clearly declining.

DILUTION AND ADMINISTRATION[10]

Dilution

- Adding Phenytoin to Dextrose or Dextrose-containing IV infusions is NOT RECOMMENDED due to a lack of solubility and the chance of precipitation.
- Phenytoin sodium should be diluted in Normal Saline, to a final concentration not less than 5 mg/ml. Do not refrigerate Phenytoin sodium once diluted.
- Begin administration immediately after dilution; complete infusion within 1 to 4 hours of preparation.

Administration

- Injected slowly, not exceeding 50 mg/min in adult or 1-3 mg/kg/min in neonates and children.

Miscellaneous

- If Phenytoin is given via a nasogastric tube or gastrostomy, tube feeds need to be held for 1 hour before and 1 hour after administration of Phenytoin.
- If Phenytoin is given to a patient on intermittent hemodialysis, the dose should be given immediately after dialysis, not before as much of the Phenytoin will be dialyzed off.

CALCULATION

1) Loading dose (LD):

$$\text{Loading Dose} = \frac{\text{Cp desired} \times \text{Vd} \times \text{BW}}{\text{S} \times \text{F}}$$

2) Incremental LD:

$$\text{Incremental LD} = \frac{(\text{Cp desired} - \text{Cp measured}) \times \text{Vd} \times \text{BW}}{\text{S} \times \text{F}}$$

3) Maintenance dose (MD):

$$\text{Dose (mg/day)} = \frac{\text{Vmax} \times \text{BW} \times \text{Cp desired (mg/L)}}{(\text{S})(\text{F})(\text{Km} + \text{Cp desired (mg/L)}}$$

4) To predict concentration from current dose:

$$\text{Cpss (mg/L)} = \frac{\text{Km} \times \text{S} \times \text{F} \times \text{Dose (mg/day)}}{(\text{Vmax} \times \text{BW}) - (\text{S})(\text{F})(\text{Dose (mg/day)})}$$

5) Clearance (CL):

$$\mathrm{CL} = \frac{\mathrm{Vm}}{\mathrm{Km} + \mathrm{Cp\ measured}}$$

6) If albumin is low (<25 g/L), use following equation:

$$\text{Cp Normal binding (mg/L)} = \frac{\text{Phenytoin Concentration (mg/L)}}{[0.9 \times \frac{\text{Patient's Albumin (g/L)}}{44}] + 0.1}$$

7) If albumin is low and CrCl is less than 10 ml/minute, use the following equation:

$$\text{Cp Normal binding} \left(\frac{\mathrm{mg}}{\mathrm{L}}\right) = \frac{\text{Phenytoin Concentration(mg/L)}}{(0.48)(0.9) \times \frac{\text{Patient's Albumin (g/L)}}{44} + 0.1}$$

8) Time to withhold therapy when concentration is toxic:

$$\mathrm{T} = \left[\mathrm{Km\ (mg/L)} \left(\ln \frac{\mathrm{Cp\ measured}}{\mathrm{Cp\ desired}}\right) + (\mathrm{Cp\ measured} - \mathrm{Cp\ desired})\right] \mathrm{x} \frac{\mathrm{Vd\ (L)}}{\mathrm{Vm\ (mg/day)}}$$

RESULT EVALUATION

CONCENTRATION	CONTRIBUTING FACTOR	RESPONSE	RECOMMENDATION
Subtherapeutic **< 10 mg/L**	• **Compliance** • **Wrong sampling time** • **Insufficient dose** • **Drug Interaction**	**Poor** **Good**	**If compliance & sampling time is satisfactory, increase the dose appropriately & resample.** **To consider incremental loading dose.** **Continue current dose**
Within normal therapeutic range **10 -20 mg/L**		**Poor** **Good**	**If compliance & sampling time is satisfactory, increase the dose (not more than max recommended)** **Continue current dose**
Potential toxic/ Toxic **> 20 mg/L**	• **Overdosage** • **Underlying disease/ factors** • **Possible drug interaction** • **Liver/Renal impairment**	**Toxic effect:** • **Hypotension** • **Excessive sedation** • **Respiratory depression**	**Withhold treatment, monitor concentration and treat signs & symptoms of toxicity (if required), then adjust dose accordingly**

The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic – pharmacodynamic parameter and clinical condition should be considered before making any recommendations.

CASE STUDY

Case 1

NS is a 35 years old lady, body weight 60 kg was admitted to the ward after experiencing status epilepticus. She was given loading dose of IV Phenytoin 900 mg stat at the Emergency Department and was prescribed IV Phenytoin 100 mg TDS in the ward. On the next day, the concentration of Phenytoin obtained was 8.17 mg/L. Her liver and renal profile was normal. Patient was still not stable and had fitting a few times in the ward. What is your recommendation for this patient?

Answer:

To check renal profile, albumin level and other drug interaction before considering incremental loading dose. Since patient's Albumin and CrCl is normal, to give another incremental loading dose for this patient.

Incremental loading dose:

$$\text{Incremental LD} = \frac{(\text{Cp desired} - \text{Cp measured}) \times \text{Vd} \times \text{BW}}{\text{S} \times \text{F}}$$

$$\text{Incremental LD} = \frac{(15\ \text{mg/L} - 8.17\text{mg/L}) \times 0.65 \times 60\ \text{kg}}{0.92 \times 1}$$

$$\text{Incremental LD} = 289.53\ \text{mg} \sim 300\ \text{mg}$$

Suggest to give incremental loading dose of IV Phenytoin 300 mg stat if patient still fit and continue with her maintenance dose IV 100 mg TDS.

Case 2

A.N is a 28 years old 55 kg man, suffering from epilepsy. He received a 300 mg ON dose of capsule phenytoin. Suddenly he felt lethargy and having slurred speech and came to casualty after having mild nystagmus. Phenytoin serum concentration randomly checked and the result recorded as 38.38 mg/L. Calculate time to withhold the dose.

Answer:

Time to withhold therapy when concentration is toxic:

$$T = \left[\text{Km (mg/L)} \left(\ln \frac{\text{Cp measured}}{\text{Cp desired}} \right) + (\text{Cp measured} - \text{Cp desired}) \right] \text{ x } \frac{\text{Vd (L)}}{\text{Vm (mg/day)}}$$

$$T = \left[4(\text{mg/L}) \left(\ln \frac{38.38 \text{ mg/L}}{15 \text{ mg/L}} \right) + \left(38.38 \frac{\text{mg}}{\text{L}} - 15\text{mg/L} \right) \right] \text{ x } \frac{0.7\text{x}55\text{kg (L)}}{7 \text{ x } 55\text{kg (mg/day)}}$$

$$T = \quad 2.714 \text{ days} \quad \sim 3 \text{ days}$$

Suggest to withhold Phenytoin dose for 3 days.

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Clinical Pharmacokinetics Pharmacy Handbook
Second Edition

SALICYLATE

Salicylate is usually being used to treat mild to moderate pain, inflammation, and fever. It is also widely used for prevention of acute coronary syndromes, acute ischaemic stroke, transient ischaemic episode and also as management of rheumatoid arthritis rheumatic fever, osteoarthritis. CPK monitoring for salicylates is mainly in poisoning cases.

KEY PARAMETERS:

Therapeutic Range	Refer text
Bioavailability (F)	Aspirin; 50 – 75% (oral) [1]
Salt Factor (S)	Not indicated
Volume of Distribution (Vd)	10 L/kg
Clearance (CL)	Aspirin: via urine (75% as Salicyluric Acid, 10% as Salicylate)
Half-life ($t_{1/2}$)	Aspirin: 15 – 20 minutes Salicylate: (300 – 600 mg) 3 hours (>1g) 5 – 6 hours;10 hours with higher doses

PHARMACOKINETIC

Bioavailability (F): [1]

Aspirin: 50 – 75% (oral)

Volume of Distribution (Vd): [1]

10 L/kg

Metabolism: [1]

Acetyl Salicylate (Aspirin): hydrolyzed to Salicylate (active) by esterase in GI mucosa, blood synovial fluid.

Salicylate: metabolized primarily by hepatic conjugation (saturable pathway)

Clearance (Cl): [1]

Aspirin: via urine (75% as Salicyluric Acid, 10% as Salicylate)

Half-life ($t^{1}/_{2}$) [1]

Aspirin (Parent drug) : 15 – 20 minutes
Salicylate (Dose dependent) : (300 – 600 mg) 3 hours
: (>1 g) 5 – 6 hours
: 10 hours with higher doses

Indication and Therapeutic Range: [1]

- Mild to moderate pain, inflammation, and fever
- Prevention of acute coronary syndromes, acute ischemic stroke and transient ischemic episode.
- Management of rheumatoid arthritis, rheumatic fever, osteoarthritis
- Salicylate serum concentration range:

Serum Salicylate Concentration (mg/L)	Effects
~ 100	Antiplatelets, antipyretic, analgesia
150 – 300	Anti-inflammatory
250 – 400	Treatment of rheumatic fever
>400 – 500	Toxicity

Renal Impairment: [1]

- CrCL <10 mL/min: avoid use
- Dialyzable: 50 – 100%

INTERACTION [1]

Salicylate may affect other drugs by:

Salicylate may increase drug concentration/effects:	Salicylate may decrease drug concentration/effects:
Alendronate Anticoagulants Carbonic Anhydrase Inhibitors Corticosteroids (systemic) Dabigatran Etexilate Heparin Hypoglycemic Agents Methotrexate NSAID (COX-2 Inhibitor) Rivaroxaban Thrombolytic Agents Ticagrelor Tositumomab and Iodine I 131 Valproic Acid and Derivatives Varicella Virus-Containing Vaccines; Vitamin K Antagonists	ACE Inhibitors Hyaluronidase Loop Diuretics Multivitamins/Fluoride (with ADE) Multivitamins/Minerals (with ADEK, Folate, Iron) Multivitamins/Minerals (with AE, No Iron) NSAID (Nonselective) Probenecid Ticagrelor

Salicylate may be affected by other drugs by:

Salicylate may be increased by:	Salicylate may be reduced by:
Agents with Antiplatelet Properties Ammonium Chloride Antidepressants (Tricyclic, Tertiary Amine) Calcium Channel Blockers (Nondihydropyridine) Ginkgo Biloba Glucosamine Herbs (Anticoagulant/Antiplatelet Properties) Influenza Virus Vaccine (Live/Attenuated) Ketorolac (Nasal & Systemic) Loop Diuretics Multivitamins/Minerals NSAID (Nonselective) Omega-3 Fatty Acids Pentoxifylline Potassium Acid Phosphate Selective Serotonin Reuptake Inhibitors Serotonin/Norepinephrine Reuptake Inhibitors Vitamin E	Corticosteroids(systemic) Ketorolac(Nasal/Systemic) NSAID (Non-selective) Floctafenine

Salicylate to be avoided using concomitantly with Influenza virus vaccine (live/attenuated) and Ketorolac (Nasal/Systemic).

SAMPLING TIME FOR TOXICITY

Sampling: [1,2,4,5]

- Sampling should be taken at least 4 hours after ingestion and repeat the salicylate concentration every 2 hours until the concentration falls.
- Nomogram can only be used for acute ingestion of non-enteric coated Aspirin, and it only indicates the severity of toxicity but cannot be used to justify the need for antidote.

MONITORING OF TOXICITY

Serum Salicylate Concentration [2,4]

- Toxicity due to chronic ingestion of aspirin is common in elderly patients taking aspirin for analgesia.
- May occur in treatment of acute rheumatic fever (80 – 100 mg/kg/day in 4 divided doses for 2 – 4 weeks).
- To do salicylate concentration on admission if signs and symptoms of toxicity are presence. Refer Appendix for Salicylate Toxicity Algorithm.

Serum Salicylate concentration and common adverse effects.

Phase	Salicylate Concentration	Clinical Features
Mild Poisoning	Adult: 300 – 600 mg/L Children/elderly: 200–450 mg/L	Lethargy, nausea, vomiting, tinnitus, dizziness
Moderate Poisoning	Adults: 600–800 mg/L Children/elderly: 450–700 mg/L	Mild features: tachypnoea, hyperpyrexia, sweating, dehydration, loss of coordination, restlessness
Severe Poisoning	Adults: > 800 mg/L Children/elderly: > 700 mg/L	Hypotension, significant metabolic acidosis after rehydration, renal failure (oliguria), CNS features e.g. hallucinations, stupor, fits, coma

- **Acid-Base Status, Volume Status and Electrolytes[4]**
  - Salicylate poisoning causes respiratory alkalosis and, by an independent mechanism, metabolic acidosis.
  - Reduction in serum bicarbonate is caused both by concomitant metabolic acidosis and by an initial respiratory alkalosis-induced bicarbonaturia.
  - Clinical severity is predicted by the acid-base status, adult patients exhibiting only respiratory alkalosis are expected to have mild toxicity, while those with a normal or near normal serum pH (7.40 ± 0.05) with underlying respiratory alkalosis and metabolic acidosis are expected to have moderate poisoning. Acidaemia (pH < 7.35) is seen in severe poisoning.
  - Euvolaemia should be achieved. Hypovolaemia can worsen Salicylate toxicity as well as impairs alkalinization of the urine.

MANAGEMENT OF TOXICITY[1]

- **Airway Protection and Respiratory Status**
  - Assess airway, breathing and circulation (ABC). Intubation only if clinically required.

- **Gastrointestinal Decontamination**
  - Administration of Activated Charcoal administration or whole bowel irrigation may be considered.

- **Urine Alkalinization**
  - Extracellular volume depletion should be corrected and diuresis should be induced with large volumes of isotonic Sodium Bicarbonate-containing IV fluids, as renal excretion of Salicylates is more dependent on urine pH than on urine flow. Urine alkalinization to a pH of 7.5 – 8.0 increases urinary excretion of Salicylates more than 10-fold and should be considered for significant salicylate toxicity in patients with intact renal function, alone or in combination with haemodialysis.
  - Haemodialysis is very effective in the treatment of patients with Salicylate toxicity since an increased fraction of free Salicylate occurs in the serum following saturation of protein binding.

Appendix: Algorithm for management of salicylate toxicity [3]

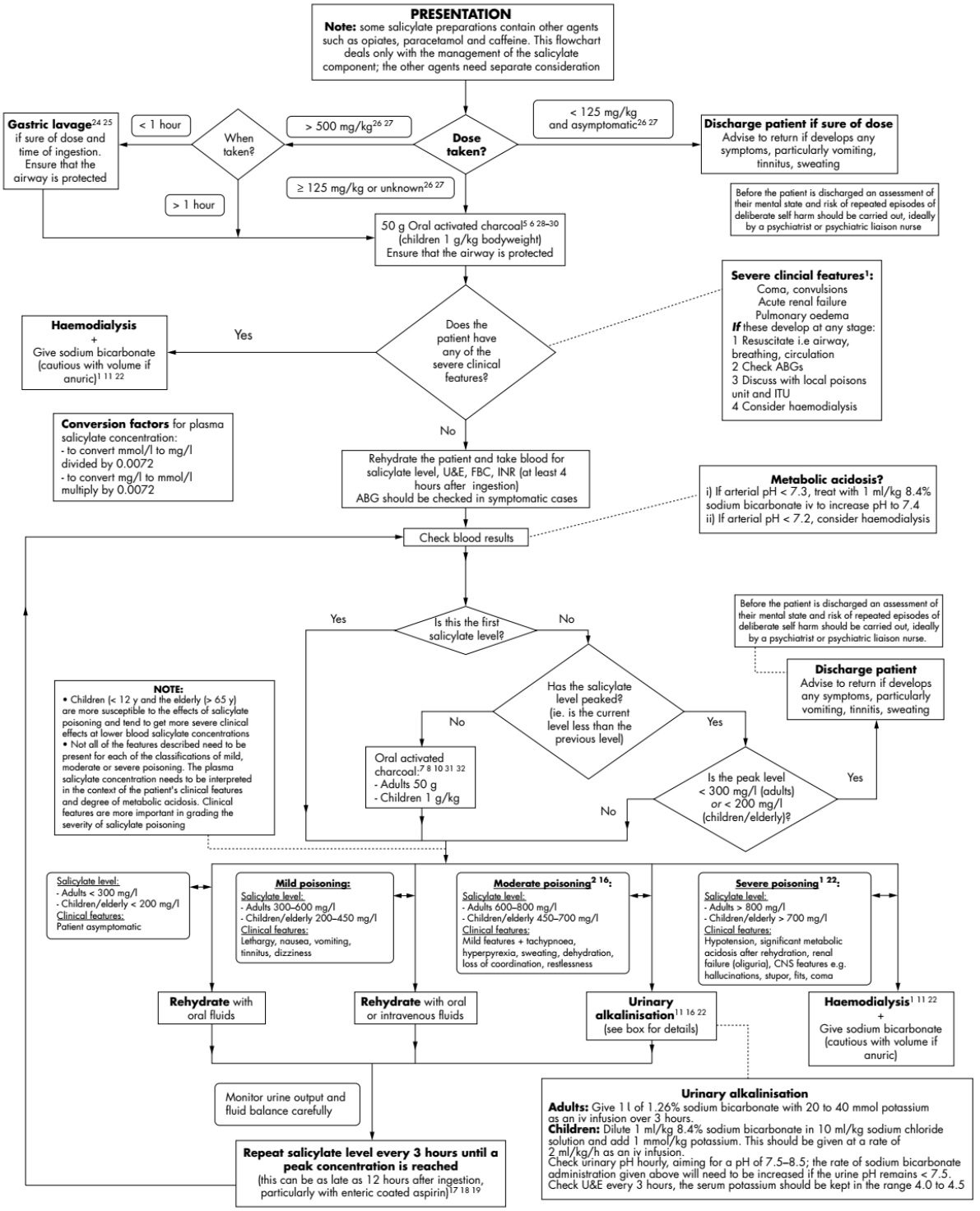

Figure 1 Flowchart for management guidance in salicylate poisoning (numbers in superscripts relate to the supporting references).

CASE DISCUSSION

A 15-years-old girl with a history of rheumatic heart disease, depression and self-harm is found surrounded by empty pill bottles approximately 1 hour after ingestion. She admits taking approximately 25 tablets of Aspirin (Acetylsalicylic Acid) 325 mg (135 mg/kg) and 2,000 mg of Ibuprofen with the intent to commit suicide. Two hours after ingestion, she notes abdominal pain but is otherwise alert, oriented, and breathing comfortably. Her initial serum Salicylate concentration is 412 mg/L 4 hours after ingestion. She is then transferred to a tertiary facility, where she notes abdominal pain, nausea, and now ringing in her ears.

On examination, she has a temperature of 36.6°C, blood pressure of 101/60 mmHg, pulse of 112 beats/min, and respiratory rate of 18 breaths/min. She answered questions appropriately. Abdominal examination elicits diffuse mild tenderness, normal bowel sounds, and no masses. Motor and sensory examination findings are normal, and she exhibits normal reflexes.

Laboratory findings reveal a serum bicarbonate level of 21 mmol/L, a negative paracetamol concentration and 6 hours after ingestion, a serum salicylate concentration of 553 mg/L. Nine and 11 hours after ingestion, the serum salicylate concentration remains at 553 mg/L. Urinalysis revealed acidic urine (pH 5), but the electrolytes remained normal.

The patient is admitted to the GICU for intravenous (IV) fluid administration, alkalinization, and observation. She becomes tachypneic. A repeated Salicylate concentrations determined 14 hours after ingestion is 635 mg/L. The established diagnosis is Salicylate poisoning. Treatment is proceeded with intravenous fluid infusion and bicarbonate replacement of 2 ml/kg/h until the serum bicarbonate concentration normalizes, urine pH is 9 and plasma Salicylate concentration reduced to 281 mg/L some 40 hours later.

On day 4 of hospitalization, clinical improvement was noted and the patient is transferred to normal medical ward for subsequent stabilization and monitoring.

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Clinical Pharmacokinetics Pharmacy Handbook
Second Edition

SIROLIMUS

Sirolimus is a macrolide antibiotic that prevent the interleukin-2 (IL-2)-driven cell cycle progression. It is usually given in combination with a calcineurin inhibitor, such as cyclosporine and prednisolone to prevent allograft rejection.

KEY PARAMETERS:

Therapeutic Range	Therapeutic concentration (general): *4 – 24 mcg/L [1,2]
Bioavailability (F)	Oral solution: 0.14 [3] Tablets: 0.18
Salt Factor (S)	1
Volume of Distribution (Vd)	Adults: 12 ± 8 L/kg
Clearance (CL)	76 – 223 ml/kg/hr[4,5]
Half-life ($t_{1/2}$)	46 - 78 hours[2,4]

* Depending on time after graft and concomitant immunosuppressants.

PHARMACOKINETIC

Bioavailability (F): [1,3,4]

Oral solution	14% , lower with high-fat meals[4]
Tablets	18% , higher with high-fat meals

Both formulations are not bioequivalent but clinically equivalent at the 2 mg dose. Sirolimus concentrations should be monitored if changes in dosage forms are made.

Volume of Distribution (Vd): [4,5]

The average volume of distribution in adults is high, which is 12 ± 8 L/kg. Sirolimus is highly uptake into blood, the blood to plasma ratio is 36.

Half-life ($t_{½}$):[2,4]

Adults	46 - 78 hours
Pediatric	6.3 - 17.3 hours
Liver impairment (Child-Pugh class A or B)	72 - 154 hours

Protein binding:[3,4,5,6,7]

Sirolimus is highly bound (92%) to human plasma protein, primarily albumin.

Metabolism:[2,4,5,6,7]

Extensively metabolized in the liver. Sirolimus is a substrate for cytochrome P450 3A4 (CYP3A4) and undergoes counter-transport by P- glycoprotein.

Elimination: [5,6,7]

Sirolimus is excreted mainly (91% in the faeces and only 2.2% eliminated in the urine.

Clearance (CL):[4,5]

Adult	**Oral solution**	**Tablets**
	123 to 223 ml/kg/hr	76 to 202 ml/kg/hr
Pediatric	218 to 682 ml/kg/hr[4]	

Pediatric demonstrated a more rapid clearance compared to adults.[4]

Similar to other immunosuppressants, sirolimus is a substrate for CYP 3A4. Hence, impairment of hepatic function is expected to affect the metabolism of sirolimus. In mild and moderate hepatically impaired patients (Child-Pugh classification of A or B), sirolimus Area Under the Curve (AUC) and half-life were increased 61% and 43% respectively, weight-normalized oral-dose clearance (CL/F) was decreased 33%.[5]

Indication and Therapeutic Range:

<table>
<tr><th colspan="2">General therapeutic range [1,2]</th></tr>
<tr><td colspan="2">4 – 24 mcg/L</td></tr>
<tr><td>Kidney transplant*</td><td>
<table>
<tr><th>With CSA</th><th>Low to moderate immunologic risk (after CSA withdrawal)</th><th>High immunologic risk (with CSA)</th></tr>
<tr><td>4 – 12 mcg/L</td><td>< 1 yr: 16 – 24 mcg/L
> 1 yr: 12 – 20 mcg/L</td><td>>1 yr: 12-20 mcg/L
≤1 yr: 10 – 15 mcg/L</td></tr>
</table>
</td></tr>
<tr><td>Combined with TAC + MMF without steroids</td><td>6 – 8 mcg/L</td></tr>
<tr><td>Substitution for TAC, combined with MMF + steroids (4-8 weeks post transplant)</td><td>8 – 12 mcg/L</td></tr>
<tr><td>Following conversion from TAC to sirolimus (>6 months post transplant - chronic allograft nephropathy)</td><td>4 – 6 mcg/L</td></tr>
<tr><td>GvHD prophylaxis in allogeneic stem cell transplant</td><td>3– 12 mcg/L</td></tr>
</table>

CSA: Cyclosporine ; TAC: Tacrolimus; MMF: Mycophenolate Mofetil; GvHD: Graft versus Host Disease

* based on HPLC methods

Target concentrations vary depending on concomitant therapy, time of post-transplant, the desired degree of immunosuppressant, adverse effect, the type of organ transplanted and immunosuppression protocols used in specific centres.

Assay results vary according to the method of assay. Results generated from HPLC UV and HPLC/MS will generally be approximately 20 % lower than immunoassay techniques for whole blood concentrations. [7]

DOSAGE

Patient	Loading Dose (mg)	Daily maintenance dose (mg)
Pediatric [8]	3 mg/m^2 STAT (Maximum: 6 mg)	1 mg/m^2 OD (Maximum MD: 2 mg/day)
Adult [2]	**Low to moderate immunologic risk** <40 kg: 3 mg/m^2 >40 kg: 6 mg STAT **High immunologic risk** Up to 15 mg STAT	**Low to moderate immunologic risk** <40 kg: 1 mg/m^2 OD >40 kg: 2 mg OD **High immunologic risk** 5 mg OD (Maximum daily dose: 40 mg)

Renal impairment:

No dosage adjustment is necessary in renal impairment.

Hepatic impairment:

Liver disease significantly increases bioavailability, reduces clearance and prolongs elimination half-life of sirolimus.

In patients with mild to moderate hepatic impairment, the maintenance dose should be reduced by approximately 33% and further reduced by half in patients with severe hepatic impairment. Loading dose is unchanged.[2]

INTERACTION

Increased SIROLIMUS concentration/effects [3]	Decreased SIROLIMUS concentration/effects [3]
Calcium channel blockers Diltiazem, Verapamil **Antibiotics** Clarithromycin, Erythromycin **HIV protease inhibitors** Indinavir, Ritonavir **Antifungal agents** Fluconazole, Itraconazole, Ketoconazole, Voriconazole **Gastrointestinal prokinetic agents** Metoclopramide **Others** Bromocriptine, Danazol, Ethinylestradiol, Methylprednisolone, Cyclosporine	**Antimicrobials** Caspofungin, Rifampicin **Anticonvulsants** Carbamazepine, Phenobarbitone, Phenytoin
Herb-drug interaction: St. John's Wort may increase the rate of CYP3A4 activity and reduce sirolimus concentrations.[2]	
Food-drug interaction: Grapefruit juice reduces CYP3A4 activity; co-administration with sirolimus should be avoided due to possible sirolimus toxicity.	
Vaccination: Immunosuppressants may affect response to vaccination. During treatment with sirolimus, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid.	

SAMPLING

Time to obtain serum sirolimus concentration (after dose initiation or adjustment): [2,3,4,5,6]

Adults : 5 – 7 Days

Pediatric : 3 – 5 Days [4]

Maintenance dose:

Oral: 30 minutes OR just before next dose

Suspected toxicity:

If toxicity is suspected, may draw out blood at any time (random).

MONITORING PARAMETERS

Patient Selection for Monitoring
a. Pediatric patients
b. > 13 years of age weighing < 40 kg.
c. Hepatic impairment [4]
d. On concurrent potent inducers of CYP3A4
e. On concurrent potent inhibitors of CYP3A4
f. If cyclosporine dose is markedly reduced/ discontinued
g. Patient receiving sirolimus plus low dose tacrolimus
h. Patients at high risk for acute rejection

Clinical monitoring parameters
a. Serum cholesterol & triglycerides (monitored once after 2-3 months, then annually) b. Blood pressure (measured at each clinical visit) c. Serum creatinine (monitored daily in the first week, 2-3 times/week (in the 1st month after initiation), weekly (2-3 months post initiation), every 2 weeks (4-6th month), monthly (7-12th month) then every 2-3 months (after 1 year) d. Urinary protein (monitored once at the 1st month, then every 3 months in the 1st year, then annually after that) e. Side effects/ADR of sirolimus f. Lymphocele, known surgical complication of renal transplantation, occurred significantly more often in a dose-related fashion in sirolimus-treated patients

ADVERSE DRUG REACTION[2]

Cardiovascular	Peripheral oedema, hypertension, oedema
Central nervous system	Headache, pain, insomnia
Dermatologic	Acne and rash
Endocrine & metabolic	Hypertriglyceridemia*, hypercholesterolaemia*, hypokalaemia
Gastrointestinal	Constipation, abdominal pain, diarrhoea, nausea
Genitourinary	Urinary tract infections
Hematologic	Anaemia and thrombocytopenia*
Neuromuscular& skeletal	Arthralgia
Renal	Serum creatinine increased
* The elevations of triglycerides and cholesterol and decreases in platelets and haemoglobin occurred in a dose-related manner	

Overdosage/Toxicology:

There is minimal experience with overdose. Only one case was reported of a patient receiving 150 mg sirolimus and the patient experienced an episode of transient atrial fibrillation. General supportive measures have been suggested in case of overdose.[2]

DILUTION AND ADMINISTRATION

Drug administration:[2]

Available tablet strength: 1 mg and 2 mg (tablet should not be crushed, chewed or split)

Oral Solution 1mg/ml (stored refrigerated):

Amber oral dose syringe should be used to withdraw solution from the bottle. Empty the correct amount of oral solution from the syringe, or if using the pouch, squeeze the entire contents of the pouch into only a glass or plastic container. Then it should be mixed with at least 60 ml of water or orange juice. No other liquids should be used for dilution. Stir vigorously, and drink at once. Refill the container with additional volume of 120 ml of water or orange juice, stir vigorously, and drink at once. Sirolimus should be taken 4 hours after cyclosporine administration with or without food consistently to minimize variability of absorption.

Dosage Adjustment Based On Serum Concentrations

Serum concentration should not be used as the sole basis for dosage adjustment, especially during the withdrawal of cyclosporine. Dosage adjustments should be based on clinical signs and symptoms, tissue biopsy and laboratory parameters.

CALCULATION

Dose Adjustment

1. Estimate CL from the obtained concentration (after steady state has achieved)

$$\text{CL (ml/hr)} = \frac{\text{S} \times \text{F} \times \text{Dose (mcg)} \times 1000}{\text{Css (mcg/L)} \times \text{Interval (hour)}}$$

2. Determine Css target and calculate the new maintenance dose.

$$\text{MD (mg)} = \frac{\text{CL (ml/hr)} \times \text{Css (mcg/L)} \times \text{Interval (hour)}}{\text{S} \times \text{F}} \times \frac{1}{1000}$$

Alternatively, assuming linear relationship between dose and concentration:

$$\text{New Dose (mg)} = \frac{\text{Desired Css}}{\text{Measured Css}} \times \text{Current dose (mg)}$$

CASE DISCUSSION

A 54-years-old man received a renal allograft with 3 Human Leukocyte Antigen (HLA) mismatches from a deceased donor. He had been treated with peritoneal dialysis for 6 years for End Stage Renal Disease (ESRD) caused by glomerulonephritis. Pre-transplant evaluation revealed normal liver chemistries. Transplant surgery passed uneventfully and the patient was hemodynamically stable. Immunosuppressive protocol included tacrolimus (0.07 mg/kg/day), mycophenolate-sodium 2 × 720 mg and steroids with basiliximab induction.

The patient experienced delayed graft function, with the last hemodialysis performed 8 days after the transplantation. On day 11 post surgery, his liver chemistries started to rise, with AST of 252 IU/L and ALT 601 IU/L. Tacrolimus trough concentration was 5.5 mcg/L, and serum creatinine was 487 µmol/L. Four days later AST increased to 421 IU/L and ALT 1242 IU/L, tacrolimus trough concentration of 7.5 mcg/L and serum creatinine of 322 µmol/L. His platelets were 278 x 10^9/L. Bilirubin was 13 µmol/L from 10 µmol/L, and LDH was 253 IU/L. The Nephrology team decided to switch from tacrolimus to sirolimus therapy 17 days after the transplantation.

Sirolimus was introduced with the loading dose of 6 mg, followed by 2 mg/day. 7 days after the drug conversion, AST fell to 225 IU/L and ALT 765 IU/L. He was discharged 6 days later with AST 110 IU/L and ALT 407 IU/L. His serum creatinine at discharge was 184 µmol/L.

Nine months later, his liver chemistries were within the normal range with serum creatinine of 175 µmol/L and sirolimus trough concentration was 14 mcg/L. There were no adverse reactions reported and the patient was tolerating well to sirolimus therapy.

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Clinical Pharmacokinetics Pharmacy Handbook
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TACROLIMUS

A macrolide antibiotic immunosuppressant that overall suppresses cellular immunity by binding to immunophilin FK506 binding protein (FKBP-12), resulting in inhibition of calcineurin phosphatase and a series of calcineurin mediated pathways (for example interleukin 2-gene transcription, cell degranulation and apoptosis) as well as prevents degradation of glucocorticoids and progesterone. Binding to T-cell receptor also suppress T-cell proliferation.[1,4]

Commonly use to prevent organ rejection after liver, heart, and kidney transplants. Off label use include Crohn's disease, Graft versus host disease (GVHD), Rejection post lung transplant, Myasthenia gravis, and refractory rheumatoid arthritis.[4]

KEY PARAMETERS:

Therapeutic Range	Trough concentration (general) [1,2]: Immediate release formulation: Month 1 to 12 : 5-20 mcg/L Extended release formulation: Month 1 to 2 : 5 -20 mcg/L >Month 2 : 5 – 15 mcg/L
Bioavailability (F)	0.25 (oral)[1,2] 1.0 (injection)[1,2]
Volume of Distribution (Vd)	Pediatric: 1.4 – 1.9 L/kg[3] Adult: 2.6 L/kg[3]
Clearance (CL)	Pediatric: 0.14 L/h/kg [3,4] Adult: 0.04 – 0.08 L/h/kg [3,4]
Half-life ($t_{1/2}$)	General: 8 – 12 hours (half-life is prolonged in patient with impaired hepatic function)[2,4]

PHARMACOKINETIC

Bioavailability (F):

Oral: Adults 7% to 32%, pediatric: 7% to 55%[3]

Volume of Distribution (Vd):

The plasma protein binding to tacrolimus is approximately 99%.[1, 5] Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and high association with erythrocytes.[5]

The distribution of tacrolimus between whole blood and plasma depends on several factors, such as haematocrit, temperature at the time of plasma separation, tacrolimus concentration, and plasma protein concentration.[6,7]

Clearance (CL):

The elimination of tacrolimus is not affected by renal or mild hepatic dysfunction.[4] Patient with severe renal dysfunction/ hepatitis C, the clearance rate is prolonged.[4]

Children have higher clearance and require higher doses of tacrolimus to achieve similar target concentration.[2]

Half-life ($t_{½}$):

In liver transplant patient [5]	
Pediatric	12.4 hours
Adult	11.7 hours
In kidney transplant patient [5]	
Adult	15.6 hours

Prolonged release formulation has an average half-life of 38 ± 3 hours in adult

Indication and Therapeutic Range:

Indications: [7]

- Prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants.
- Use concomitantly with adrenal corticosteroids.
- Use in conjunction with azathioprine or mycophenolate mofetil for kidney and heart transplants.

Limitations of uses: [6,7]

- Do not use concurrently with cyclosporine.
- Intravenous use only reserved for patient who cannot tolerate orally.
- For liver and heart transplants, use with sirolimus is not recommended.
- For kidney transplant, use with sirolimus has not been established.

<table>
<tr><th colspan="2">General therapeutic range[1,2,6]</th></tr>
<tr><td colspan="2">5 – 20 mcg/L</td></tr>
<tr><td>Liver transplant[1]</td><td>Months 1 – 12: 5 – 20 mcg/L</td></tr>
<tr><td>Kidney transplant[6]</td><td>
<table>
<tr><th>Time (months post-transplant)</th><th>Low rejection risk (mcg/L)</th><th>Moderate rejection risk (mcg/L)</th><th>High rejection risk (mcg/L)</th></tr>
<tr><td>0 – 6</td><td>6 – 12</td><td>8 – 12</td><td>8 – 15</td></tr>
<tr><td>7 – 12</td><td>5 – 8</td><td>5 – 10</td><td>6 – 12</td></tr>
<tr><td>>12</td><td>4 – 8</td><td>5 – 10</td><td>6 – 12</td></tr>
</table>
</td></tr>
<tr><td>Heart transplant[1]</td><td>Months 1 – 2 : 10 – 15 mcg/L
Months 3 - 6 : 8 – 12 mcg/L
Months >6 : 5 – 10 mcg/L</td></tr>
<tr><td>Crohn's Disease[1]</td><td>10 – 20 mcg/L</td></tr>
<tr><td>Lung Transplant[1]</td><td>5 – 15 mcg/L</td></tr>
<tr><td>Myasthenia Gravis[1]</td><td>8 -9 mcg/L</td></tr>
<tr><td>Prevention of graft versus host disease[1]</td><td>10 -20 mcg/L</td></tr>
</table>

DOSAGE

Pediatric: [7]

Age	Liver transplantation (Starting within 12 hours of transplantation)		Kidney transplantation (Starting within 24 hours of transplantation)		Heart transplantation (without antibody induction, starting 12 hours of transplantation)		Heart transplantation (following antibody induction, starting within 5 days of transplantation)
	Oral	IV infusion	Oral	IV infusion	Oral	IV infusion	Oral
Neonate	Initial 0.15 mg/kg BD	0.05 mg/kg over 24 hours for up to 7 days then transfer to oral therapy	Initial 0.15 mg/kg BD	0.075 – 0.1 mg/kg over 24 hours for up to 7 days then transfer to oral therapy	Initial 0.15 mg/kg BD (8-12 hours after discontinuation of IV infusion)	0.03 – 0.05 mg/kg over 24 hours for up to 7 days then transfer to oral therapy	Initial 0.05 – 0.15 mg/kg BD
1 month – 18 years old	Initial 0.15 mg/kg BD	0.05 mg/kg over 24 hours for up to 7 days then transfer to oral therapy	Initial 0.15 mg/kg BD [a]	0.075 – 0.1 mg/kg over 24 hours for up to 7 days then transfer to oral therapy	Initial 0.15 mg/kg BD (8-12 hours after discontinuation of IV infusion)	0.03 – 0.05 mg/kg over 24 hours for up to 7 days then transfer to oral therapy	Initial 0.05 – 0.15 mg/kg BD

[a]A lower initial dose of 0.1mg/kg twice daily has been used in adolescents to prevent very high 'trough' concentration.

Adult: [1]

Liver transplantation		Kidney transplantation		Heart transplantation	
Oral	**IV infusion**	**Oral**	**IV infusion**	**Oral**	**IV infusion**
0.10 – 0.20mg/kg/ day in two divided doses (start approximately 6 hours after the completion of liver transplant)	0.01 – 0.05 mg/kg/ day	0.15 – 0.30 mg/kg/ day in two divided doses (start approximately within 24 hours of kidney transplant)	0.05 – 0.10mg/ kg/ day	0.075 mg/kg/ day in two divided doses	Initial 0.01 mg/kg/ day

Renal impairment: [1,10]

Patients should receive the lowest effective dose of the recommended intravenous and oral dosing ranges.

Haemodialysis	No dosing adjustment is needed. Not removed by haemodialysis, no supplemental dose is needed.
Peritoneal dialysis	No dosing adjustment is needed. Significant drug removal is unlikely based on psychochemical characteristics.
Continuous renal replacement therapy (CRRT)	No dosing adjustment is needed.

Hepatic impairment: [6,7]

Dose reduction is not necessary. Close monitoring is needed as the half-life of the drug is prolonged and the clearance reduced after intravenous administration. The bioavailability of tacrolimus is increased after oral administration.

INTERACTION: [2,5,9]

Tacrolimus is metabolized by CYP3A4 and is a substrate for P-glycoprotein.

Drug that inhibit CYP3A4 and P-glycoprotein	Drug that induce CYP3A4 and P-glycoprotein
Calcium channel blockers Diltiazem Verapamil Amlodipine **Antibiotics** Clarithromycin Erythromycin **Antifungal agents** Fluconazole Itraconazole Ketoconazole **Protease inhibitors** Indinavir Ritonavir **Prokinetic agents** Metoclopramide **Others** Bromocriptine Danazol Ethinyl estradiol Grapefruit juice Methylprednisolone	**Antimicrobials** Caspofungin Nafcillin Rifampicin **Anticonvulsants** Carbamazepine Phenobarbital Pheytoin Primidone **Others** St. John's wort

SAMPLING[2,5,6,12]

Time to monitor serum concentration (at steady state):

When to obtain serum tacrolimus concentration (after dose initiation or adjustment)	
Trough sample: 30 minutes before dose	• Trough concentration should be assessed 3 – 5 days after initiation of therapy, after a dosage adjustment, or after discontinuation or initiation of known CYP3A4 inhibitors or inducers. • Sample should be collected into ethylene-diamine-tetra-acetic acid [EDTA] tube. • Sampling time should be consistent during monitoring period

Suspected toxicity:

If toxicity is suspected, blood sample may be drawn at any-time (random sampling).

Assay Measurement:

Plasma:	Processed at 37ºC is viable but require highly sensitive assay due to lower concentrations measured.
Whole Blood:	Preferred method as faster processing time and less sensitive assay can be used.

**Whole blood concentration is 10-30 times higher than plasma concentration.*

TDM after formulation conversion:

Dose conversion between immediate release and prolonged release is on the ratio of 1:1 (mg : mg).

After formulation conversion, for kidney and liver transplant patients, minimum dosage adjustment is needed. For heart transplant patients, Clinical Pharmacokinetic monitoring is required to ensure similar systemic exposure is maintained.

MONITORING PARAMETER[1,5]

Constant monitoring of renal function, liver function, serum electrolytes, glucose and blood pressure (3 times/ week) during first few weeks of treatment.

For IV tacrolimus, signs and symptoms of anaphylaxis should be monitored during the first 30 minutes of infusion, and frequently thereafter.

The frequency of monitoring of the following parameters can gradually decrease as patient stabilises.

- Blood pressure (hypertension is a common side effect; proper antihypertensive agents selection is required)
- ECG periodically during treatment, especially in patients at risk for QT prolongation (concomitant use of other QT prolongation drugs or CYP3A inhibitors)
- Blood glucose level; frequently
- Serum potassium levels (especially in patients receiving other medications associated with hyperkalaemia, e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors (ACE) and angiotensin receptor blockers)
- Renal function; frequently (particularly when use in high dose, dose reduction is needed. Consideration change to other immunosuppressant should be made if patient unresponsive to dosage adjustment of tacrolimus.)
- Liver function; frequently
- Neurotoxicity (particularly when use in high dose).
    - Posterior reversible encephalopathy syndrome [PRES] (most severe neurotoxicity). Symptoms of PRES: headache, altered mental status, seizures, visual disturbances, and hypertension. Diagnosis may be confirmed by radiological procedure. Immediate dose reduction is advised.

ADVERSE DRUG REACTION[1,5]

Adverse drug reaction (occurrence ≥ 15 %)	
Cardiovascular	hypertension, oedema, chest pain, pericardial effusion
Central nervous system	headache, insomnia, pain, fever, dizziness
Dermatological	pruritus, rash
Endocrine & metabolic	hypophosphataemia, hypomagnesemia, hyperglycaemia, hyperkalaemia, hyperlipidaemia, hypokalaemia, diabetes mellitus
Gastrointestinal	diarrhoea, abdominal pain, nausea, constipation, anorexia, vomiting, dyspepsia
Genitourinary	urinary tract infection
Haematological	anaemia, leukopenia, leukocytosis, thrombocytopenia
Renal	abnormal kidney function, creatinine increased, BUN increased, oliguria
Hepatic	liver function test abnormal, ascites

Overdosage/Toxicology: [7]

Limited data on cases with tacrolimus overdoses.

A chronic overdose is known to cause nephrotoxicity (elevation of serum creatinine and decrease in urine output). Acute overdoses of up to 30 times the therapeutic dose have occurred with tacrolimus and almost all cases have been asymptomatic and recovery uneventful.

In severe cases, it may manifest as seizure, delirium or coma.

Management of overdosage/toxicology: [13]

- Treatment is supportive and symptomatic
- Consider activated charcoal following oral ingestion. Emesis is not indicated.
- Hypertensive disorder: Mild/ moderate asymptomatic hypertension usually does not require treatment. Nitroprusside or nitroglycerin may be considered with severe episodes.
- Seizure: IV benzodiazepines, barbiturates.
- Haemodialysis: Based on high protein binding, large molecular weight, and extensive partitioning of tacrolimus into red blood cells, haemodialysis is not anticipated to be effective following overdose.
- Monitoring of patient: Monitor vital signs and neurological status.
- Obtain serial full blood count (FBC) with differential and electrolytes following a significant exposure.
- Monitor renal and hepatic function after significant overdose.

DILUTION AND ADMINISTRATION

Dilution of drug: [1]

Dilution of drug	Dilute with Dextrose 5% (D5W) or Normal saline to a final concentration between 0.004 mg/ml and 0.02 mg/ml Diluted solution should be stored in a glass or polyethylene containers and should be discarded after 24 hours. Diluted solutions should not be kept in polyvinyl chloride (PVC) container due to decreased stability and potential for extraction of phthalates.

Drug administration: [1,3]

Drug administration	
Oral	Administer on empty stomach; be consistent with timing and composition of meals. The presence of food, particularly high-fat meal, decreases the rate and extent of tacrolimus absorption.
Intravenous infusion	To be administered as continuous infusion. Conversion from IV to oral tacrolimus is recommended once patient can tolerate orally. This normally occurs within 2 – 3 days. The first of oral therapy should be given 8 – 12 hours after discontinuing the IV infusion.

CALCULATION[4]

A) Dose Initiation

1. Estimate clearance

$$\text{CL (L/hour)} = \text{CL (L/kg/hour)} \times \text{BW(kg)}$$

Mean Tacrolimus clearance (Adult) = 0.06 L/h/kg

Tacrolimus clearance (Pediatric) = 0.14 L/h/kg

2. Determine Css target and calculate maintenance dose

$$\text{MD (mg)} = \frac{\text{CL } (L/hour) \times \text{Css target } (mcg/L) \times \text{Interval (hour)}}{\text{S} \times \text{F}} \times \frac{1}{1000}$$

S = 1.0

F = 0.25 (oral); 1.0 (injection)

B) Dose Adjustment

1. Estimate CL from the obtained concentration

$$\text{CL (L/hr)} = \frac{\text{S} \times \text{F} \times \text{Dose (mcg)}}{\text{Css (mcg/L)} \times \text{Interval(hour)}}$$

2. Determine Css target and calculate a new maintenance dose

$$\text{MD (mg)} = \frac{\text{CL } (L/hour) \times \text{Css target } (mcg/L) \times \text{Interval(hour)}}{\text{S} \times \text{F}} \times \frac{1}{1000}$$

CASE DISCUSSION

A 28 years old male patient underwent cadaveric kidney transplant at the age of 17. His comorbidities include hypertension, dyslipidemia and chronic colitis since the age of 26. Patient was started with single immunosuppressant (tacrolimus 2 mg OM, 1 mg PM) after kidney transplantation, with mycophenolate mofetil 500 mg BD added after a year of transplantation due to high risk of graft rejection. His concurrent medications include bisoprolol 2.5 mg ON, prednisolone 7.5 mg OD and deslansoprazole 30 mg OD.

Patient was stable with tacrolimus (immediate release) 0.5 mg OM, 1 mg PM from the fifth year to tenth year post-transplant, with trough concentrations between 4.9 mcg/L and 6.7 mcg/L. However, on the tenth year post-transplant, patient had multiple admissions as describe below:

- On July of the tenth year;
  - Patient was admitted to hospital with stool culture positive for *Clostridium difficile* (treated with IV Metronidazole and Ceftriaxone). Upon discharge, tacrolimus regimen was maintained at **0.5 mg OM/1 mg PM** with concentration at 6.1 mcg/L.

- However on the following month (August);
  - Tacrolimus concentration raised to 8.3 - 9.7 mcg/L for three readings, hence tacrolimus was reduced to **0.5 mg BD**, with new concentration around 5.0 – 6.0 mcg/L for three subsequent monitoring.

- Later in October;
  - Patient was admitted with pyelonephritis complicated with acute kidney injury (Haemodialysis was done as supportive treatment). During this admission, tacrolimus regimen was maintained at 0.5 mg BD. However tacrolimus concentration fluctuated from as high as 15 mcg/L to as low as 2.3 mcg/L, possibly due to the influence of acute kidney injury (AKI). Successively, tacrolimus concentration was stabilised at 6.2 mcg/L upon discharge, hence tacrolimus regimen **(0.5 mg BD)** was maintained.

- Patient was readmitted six days later;
  - For chronic diarrhoea secondary to *Clostridium difficile* and AKI secondary to sepsis with gastrointestinal loss (HPE suggestive of Chronic Colitis). Last recorded tacrolimus concentration was 5.2 mcg/L prior to admission. The concentrations were fluctuated to as low as 3.2 mcg/L during this admission; hence tacrolimus dose was titrated to **1 mg OM, 0.5 mg PM** with tacrolimus concentration of 5.7 mcg/L upon discharge. The length of hospitalisation for this admission was 1 month.

- Seven days after discharged, patient was readmitted for AKI. There was a concern that the difference in tacrolimus morning and evening dose would cause fluctuation in concentration, of which the existence of high pre concentration would be masked by monitoring the pre morning dose (since night dose was the lower dose compared to morning dose). Further tacrolimus concentration monitoring showed that pre evening dose has a higher concentration of 7.0 mcg/L compared to pre morning dose which was measured at 4.9 mcg/L.

In view of patient's multiple admissions for AKI, with wide fluctuation between morning and evening concentrations that might pose further risk for graft versus host disease in this patient, the immediate-release formulation was switched to **prolonged-release tablet, 1.5 mg OD** with resulted tacrolimus concentration of 3.8 mcg/L. Consequently, tacrolimus was further **titrated up to 2 mg OD.** This dose was maintained to date, with concentration stabilised at around 5.8 – 7.2 mcg/L.

Subsequently, ultrasound scan were done in January and December of the following year and the findings revealed stable graft with neither infection nor obstructive uropathy of the transplanted kidney.

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THEOPHYLLINE

Theophylline is a methylxanthine compound that is historically used to treat bronchial asthma, chronic obstructive pulmonary disease (COPD), and premature apnea owing to its bronchodilatory effect. Treatment of asthma with sustained-release theophylline has been reported as having weak efficacy with side effects being common. IV Aminophylline and theophylline are not recommended to be used in management of asthma exacerbations due to their poor efficacy and safety profile.[9] On the contrary, a modest bronchodilator effect with sustained-release theophylline was observed compared to placebo in the treatment of stable COPD. However, IV Aminophylline is not recommended due to significant side effects. [10]

For the treatment of premature apnea, most clinicians prefer to use caffeine instead of theophylline because of smoother apnea control and lesser adverse effects.[2] Although theophylline is no longer preferred as first-line agents in the management of these respiratory diseases, knowledge of its pharmacokinetics can help to ensure that the drug is used safely in those patients whom its use is appropriate.

KEY PARAMETERS [1]:

Therapeutic range	5 – 20 mg/L *
Bioavailability (F)	1
Salt Factor (S)	1, Aminophylline: 0.8
Volume of Distribution (Vd)	0.5 L/kg#
Clearance (CL)	0.04 L/kg/hr#
Half-life ($t_{1/2}$)	8 hours#

*Subject to specific indication

#Adults with no liver impairment/concomitant disease/disorders, for detailed information refer following sections

PHARMACOKINETIC

Aminophylline [2]

Ethylenediamine salt of theophylline

- Anhydrous aminophylline contains ~85% theophylline

- Aminophylline dehydrate contains ~80% theophylline

Bioavailability [1,2,4]

- Oral: Rapid and complete (90 – 100% bioavailability), dosage-form dependent
- Food does not affect absorption of fast-release products and most sustained-release products; however, food may induce a sudden release (dose-dumping) of once-daily sustained release product.

Volume of Distribution [1,3]

Distributes poorly into body fat, dose should be based on ideal body weight.

Neonates (< 4 weeks)	Infants (4 weeks – 1 year)	Children (≥ 1 year), adolescents, adults, elderly
0.8 L/kg	0.5 – 0.7 L/kg	0.5 L/kg

Protein Binding [1,2]

- 40%, primarily to albumin
- Unbound fraction of theophylline is freely distributed into body fluid, cerebrospinal fluids, placenta and breast milk.

Elimination [1,2,3]

- Elimination: Liver (>90%), ~10% unchanged in urine
- Primarily via CYP1A2 enzyme system, secondary: CYP3A, CYP2E1
- Follows non-linear pharmacokinetics; however linear pharmacokinetics are used to compute dose and estimate serum concentrations in clinical setting.

Clearance (CL) [1]

Based on lean or ideal body weight:

Premature neonates	Term infants	Pediatric	Adults
PNA 1 – 30 days: 0.02 L/kg/hr	PNA 1 week: 0.03 L/kg/hr	1 – 8 years: 0.09 L/kg/hr	16 – 60 years healthy, non-smokers: 0.04 L/kg/hr
PNA 25 – 57 days: 0.04 L/kg/hr	PNA 6 months: 0.06 L/kg/hr	9 – 12 years: 0.07 L/kg/hr	Elderly (> 60 years) non-smokers with normal cardiac, liver, and renal function: 0.025 L/kg/hr
	PNA 9 months: 0.09 L/kg/hr	13 – 15 years: 0.05 L/kg/hr	

PNA: Postnatal age

Several clinical factors also influence theophylline clearance (refer to 'Factors Affecting Clearance' section).

Half-life ($t_{½}$) [1,2,3,6]

The half-life for theophylline depends on age and renal function. Half-life for normal adults without disease states/conditions with normal liver function: 8 hours (range: 6 – 12 hours). [2]

Condition	Half-life mean (± SD)
Premature neonates	
PNA 1 – 30 days	31 hours (± 12)
PNA 31 – 60 days	20 hours (± 5)
Term infants	
PNA 1 week	18 hours (± 1)
PNA 6 months	7 hours (± 1)
PNA 9 months	4 hours (± 1)
Pediatric	
1 – < 9 years	3 hours (± 1)
9 – 15 years	4 hours (± 2)
Adults	
16 - 60 years healthy, non-smoking asthmatics	8 hours (± 2)
Elderly (>60 years) non-smokers with normal cardiac, liver, and renal function	10 hours (± 2)

Indication and Therapeutic Range:

Asthma / COPD: 10 – 20 mg/L [1,2,3]

- A target of 5 – 15 mg/L enhances safety and does not compromise efficacy
- Improvement in respiratory function can be observed as low as 5 mg/L
- Clinical response to concentrations between 5-15 mg/L should be assessed before higher targets are used
- Many patients requiring chronic therapy will achieve sufficient response with low likelihood of adverse effects at 8 -12 mg/L

Apnea / Bradycardia in Neonates: 5 – 10 mg/L [1]

- Many neonates respond at low concentrations; can be increased in increments of 3 mg/L as necessary

Ventilator Weaning in Neonates: 5 – 20 mg/L [1]

- Studies supporting desired theophylline concentration are limited; some suggest that > 8 mg/L is required to enhance diaphragmatic contractility and promote relaxation of respiratory muscles

*Conversion factor: mg/L x 5.55 = µmol/L

DOSAGE

Adult [4,5]

Loading Dose (based on Ideal BW):

If no theophylline received within the previous 24 hours

LD: 4.6 mg/kg of immediate-release theophylline **or** 5.7 mg/kg of aminophylline (over 30 minutes) to achieve a target concentration of 10 mg/L

If theophylline has been administered/received in the previous 24 hours

Check for serum theophylline concentration

LD = (Concentration desired – Concentration measured) x V_d

Maintenance Dose (based on Ideal BW):

Group	IV Aminophylline	Oral Theophylline
Adults (16 – 60 years healthy, non-smokers)	0.5 mg/kg/hr; max 1125 mg/day*	Initially 300 mg/day in 3 - 4 divided doses, titrate up to 600 mg/day Theophylline SR: 250 mg every 12 hourly
Elderly (>60 years)	0.38 mg/kg/hr; max 500 mg/day*	Do not exceed 400 mg/day
Hepatic impairment	0.25 mg/kg/hr	As per adult dosing; dose should be adjusted to serum concentrations
Smokers (>16 years old, cigarette or marijuana use)	0.875 mg/kg/hr	
Cardiac decompensation, cor pulmonale	0.25 mg/kg/hr; max 400 mg/day*	

* Unless serum concentrations indicate need for larger dose

- Dose may be increased by ~25% at intervals of 2 – 3 days if the drug is tolerated.
- If dose is >600 mg/day, titrate dose according to serum theophylline concentrations.

Pediatric [4,5,7,8]

Loading Dose (based on Ideal BW):

If no theophylline received within the previous 24 hours

IV Aminophylline 5.8 mg/kg[4] – 10 mg/kg[7] over 30 – 60 minutes

If theophylline has been administered/received in the previous 24 hours

Check for serum theophylline concentration

LD = (Concentration desired – Concentration measured) x V_d

Maintenance Dose (based on Ideal BW):

IV Aminophylline 1.5 mg/kg – 3 mg/kg every 8 – 12 hours [8]

OR

Group	IV Aminophylline	Oral Theophylline
Neonates 1st week of life	2.5 mg/kg every 12 hourly	-
Neonates 2nd week of life	3 mg/kg every 12 hourly	-
Neonates 3rd week of life – Infants 12 months	[(0.12 x age in weeks) + 3] every 8 hourly	Term infants: [(0.2 x age in weeks) + 5] x BW in kg, in divided doses every 8 hours
Children >1 year	<35 kg: 1 mg/kg/hr or 6 mg/kg every 6 hourly	<45 kg: 10 – 14 mg/kg/day initially, taper up to 20 mg/kg/day; max 600 mg/day
Children <16 years (non-smokers)	>35 kg: 0.7 mg/kg/hr or 4 mg/kg every 6 hourly	>45 kg: Refer adult dosing
Children 12 – 16 years (smokers)	0.88 mg/kg/hr	

- Sustained-release oral formulation for children ≥ 1 year old, dose as per immediate-release formulation

Renal Impairment [1,2,4,5]

- **Neonates:** ~50% of the theophylline dose is excreted unchanged in the urine, 7 – 10% converted to caffeine (active metabolite, $t_{1/2}$ = 100 hours). If urine output <2 ml/kg/hr, dosing adjustment may be required and frequent monitoring is recommended.
- **Infants 1 – 3 months:** Consider dose reduction and frequent monitoring.
- **Infants >3 months, children, adolescents, adults:** 10% excreted by the kidney unchanged, no dosage adjustment necessary.
- Theophylline is dialyzable; doses should be held until after dialysis is complete if possible. Patients may require dosage adjustments to account for increased elimination during dialysis.
- Theophylline is not appreciably removed by peritoneal dialysis.

INTERACTION

Increase theophylline clearance	CL Factor	Decrease theophylline clearance	CL Factor
Condition			
Smoking (tobacco)	1.6	Severe COPD (with cor pulmonale)	0.8
Cystic fibrosis	1.5	Sepsis with multiorgan failure	0.7
Hyperthyroid	1.2	Hypothyroid	0.6
		Acute pulmonary edema	0.5
		Acute viral illness (children 9 – 15 years)	0.5
		Hepatic cirrhosis, Acute hepatitis	0.5
		Congestive heart failure	0.5
		Pneumonia	0.4
Drug			
Phenytoin	1.6	Allopurinol (≥600 mg/day)	0.8
Phenobarbitone	1.3	Erythromycin	0.75
Rifampicin	1.3	Ciprofloxacin	0.7
		Frusemide	0.7
		Ticlopidine	0.65
		Cimetidine	0.6
		Propranolol	0.6
		Verapamil	0.5
		Influenza vaccines	0.5
		Fluvoxamine	0.3

The products for all factors that are present must be multiplied by the average clearance value. [1,3]

SAMPLING

When to monitor theophylline concentrations: [1,3]

When to monitor	Indication
Neonates	
2 hours after first loading dose	To calculate V_d (if desired)
Every 4 – 7 days	To calculate clearance and evaluate need for dosage adjustments (clearance can change quickly in this population)
Infants, children, adults, and geriatrics	
30 minutes after first loading dose	• To determine maintenance dose • To calculate V_d for additional loading dose
12 – 24 hours after initiation of maintenance dose	• To determine if serum concentration is adequate • To determine if the drug is accumulating rapidly
3 days after initiation, subsequently every 1 – 3 days	• To evaluate need for dosage adjustment • To determine if clearance is changing
Every 4 – 7 days once patients are stabilized	• To evaluate need for dosage adjustment • To determine if clearance is changing
Every 1 – 6 months	• Monitoring in stable patients
Immediately	• When there are signs or symptoms of toxicity • Suspicion of lack of efficacy

- In patients receiving any dosage form of theophylline other than continuous infusion, routine monitoring of theophylline concentrations is probably most reliable when **troughs** are obtained (0 – 30 minutes before next dose is served).

MONITORING PARAMETERS

The following are monitoring parameters for theophylline efficacy. [1]

Asthma or COPD:

- Decrease in severity of wheezing and rales
- Normalization of respiratory rate
- Improvement of FEV_1
- Decrease in ventilator support required

Apnea or bradycardia in neonates:

- Decrease in number and depth of apneic and bradycardic episodes
- Normalization of heart rate
- Decrease in ventilator support required

ADVERSE DRUG REACTION

Monitoring for concentration-related adverse effects: [1]

Serum concentration	Adverse effect
>20 mg/L	Nausea, vomiting, diarrhea, tachycardia, headache, irritability, insomnia, tremor
>35 mg/L	Hyperglycemia, hypokalemia, hypotension, cardiac arrythmias, hyperthermia, seizures, brain damage, and death

In neonates receiving theophylline for apnea, bradycardia, or ventilator weaning, the following adverse effects may indicate toxicity:

- Tachycardia (HR >180 bpm)
- Irritability
- Seizures
- Vomiting (coffee-ground appearance)

Overdosage/Toxicology: [2,5]

- There is no specific antidote for theophylline toxicity.
- For overdose of oral theophylline, activated charcoal should be administered. Multiple doses are recommended to increase elimination of theophylline from plasma, but administration may be difficult in patients with severe toxicity/persistent vomiting.
- Treat nausea with antiemetics and administer IV fluids. Avoid phenothiazine antiemetics (promethazine, prochlorperazine) as they may decrease seizure threshold.
- Monitor electrolytes, vital signs, and mental status.
- Patients should be placed on cardiac monitoring.
- In severe theophylline toxicity, increased sympathomimetic effects may be observed. The primary treatment is sedation with benzodiazepines; high doses may be required.

- Significant tachycardia should be treated with IV Esmolol, which can paradoxically improve BP in severely tachycardic patients.
- Hypotension should be treated with IV fluids.
- Haemodialysis should be performed in patients with severe toxicity, and patients with high serum theophylline concentrations (80 – 100 mg/L after acute overdose, 40 – 60 mg/L with chronic toxicity).
- Serial serum theophylline concentrations (every 1 to 2 hours) may be taken until concentration begins to fall. Sustained-release formulation may delay peak level for up to 24 hours.

DILUTION AND ADMINISTRATION

Dilute in Normal Saline or Dextrose 5% [6]
(refer product information leaflets for brand-specific recommendations)

Loading & Maintenance Dose

Dose	Dilution	Infusion time
0 – 250 mg	50 ml	30 minutes
251 – 500 mg	100 ml	30 minutes

Continuous Infusion

Dose	Dilution	Infusion time
500 mg	500 ml	Titrate

Fluid Restriction

Dose	Dilution	Infusion time
500 mg	250 ml	Titrate

- Stable for 1 day at room temperature
- IM administration is not recommended

CALCULATION

A) Dose Initiation [3]

Loading dose: Intravenous

1. Estimate volume of distribution (V_d):

$$\text{Vd (L)} = (0.5\ \text{L/kg}) \times \text{Ideal BW (kg)}$$

2. Determine the C_p target and calculate loading dose (LD):

$$\text{LD (mg)} = \frac{\text{Vd (L)} \times \text{Cp target (mg/L)}}{\text{S} \times \text{F}}$$

3. If patient has already received theophylline in the previous 24 hours, serum theophylline concentration should be checked before starting on loading dose.

$$\text{LD (mg)} = \frac{\text{Vd (L)} \times [\text{Cp target} - \text{Cp obtained}]\ (\text{mg/L})}{\text{S} \times \text{F}}$$

Maintenance dose: Oral / Intravenous

1. Estimate clearance (CL):

$$\text{CL (L/hr)} = \text{CL (L/kg/hr)} \times \text{Ideal BW(kg)}$$

$$\text{Total CL (L/hr)} = \text{CL (L/hr)} \times \text{CL factor} *$$

$$* \text{ refer to table in Factors Affecting Clearance}$$

2. Determine C_{pss} target and calculate maintenance Dose (MD):

$$\text{MD (mg)} = \frac{\text{Total CL (L/hr)} \times \text{Cpss target (mg/L)} \times \text{Interval (hr)}}{\text{S} \times \text{F}}$$

B) Dose Adjustment [3]

1. Estimate clearance (CL) from the obtained steady-state concentration:

$$\text{CL (L/day)} = \frac{\text{S} \times \text{F} \times \text{Dose (mg/day)}}{\text{Cpss (mg/L)}}$$

2. Determine C_{pss} target and calculate the new maintenance dose (MD):

$$\text{MD (mg)} = \frac{\text{CL (L/day)} \times \text{Cpss target (mg/L)} \times \text{Interval (day)}}{\text{S} \times \text{F}}$$

RESULT EVALUATION

CONCENTRATION	CONTRIBUTING FACTOR	RESPONSE	RECOMMENDATION
Subtherapeutic **<10 mg/L**	• **Compliance** • **Wrong sampling time** • **Insufficient dose** • **Drug/disease interaction**	**Poor** **Good**	**If compliance & sampling time is satisfactory, give incremental loading dose STAT (for patient in ward), then increase the dose if required or continue with current dose & resample** **Continue current dose**
Within normal therapeutic range **10 – 20 mg/L**		**Poor** **Good**	**Determine other factors that may contribute to poor response and treat accordingly** **Continue current dose**
Potential toxicity/ Toxic **>20 mg/L**	• **Overdosage** • **Underlying disease/ factors** • **Possible drug/disease interaction**	**Toxic effect:** • **Tachyarrythmias (including sinus tachycardia)** • **Ventricular arrythmia** • **Seizures/ convulsions** • **Hypokalemia**	**Withhold treatment, monitor level and treat signs & symptoms of toxicity (if required), then adjust dose accordingly**

The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic – pharmacodynamic parameter and clinical condition should be considered before making any recommendations.

CASE DISCUSSION

MSA, a 65-years-old gentleman (BW 80 kg, Height 170 cm) is admitted in the emergency department with acute exacerbation of chronic obstructive pulmonary disease secondary to community acquired pneumonia that is unresponsive to first-line treatments. He was previously not on theophylline, does not have any other concomitant disease, but is a cigarette smoker.

To estimate loading dose of IV Aminophylline that will produce a concentration of 10 mg/L:

1) Calculate IBW. For this patient, IBW = 66.1 kg

2) Estimate volume of distribution

$$\begin{aligned} \text{Vd (L)} &= (0.5\ \text{L/kg}) \times \text{ Ideal BW (kg)} \\ &= (0.5\ \text{L/kg}) \times \ 66.1\ \text{kg} \\ &= 33.05\ \text{L} \end{aligned}$$

3) Calculate loading dose

$$\text{LD (mg)} = \frac{\text{Vd (L)} \times \text{Cp target (mg/L)}}{\text{S} \times \text{F}}$$

$$= \frac{33.05\ \text{L} \times 10\ \text{mg/L}}{0.8 \times 1}$$

$$= \ 413\ \text{mg}$$

Therefore, a loading dose of IV Aminophylline 400 mg can be given.

To estimate maintenance dose for this patient:

1) Estimate clearance

$$\text{CL (L/hr)} = \text{CL (L/kg/hr)} \times \text{Ideal BW(kg)}$$

$$= 0.04 \text{ L/kg/hr} \times 66.1 \text{ kg}$$

$$= 2.644 \text{ L/hr}$$

CL factor for this patient: Smoking = 1.6, Pneumonia = 0.4

$$\text{Total CL (L/hr)} = \text{CL (L/hr)} \times \text{CL factor}$$

$$= 2.644 \text{ L/hr} \times 1.6 \text{ x } 0.4$$

$$= 1.692 \text{ L/hr}$$

2) Calculate maintenance dose to maintain a steady-state concentration of 10 mg/L

$$\text{MD (mg)} = \frac{\text{Total CL (L/hr)} \times \text{Cpss target (mg/L)} \times \text{Interval (hr)}}{\text{S} \times \text{F}}$$

$$= \frac{1.692 \text{ L/hr} \times 10 \text{ mg/L} \times 8 \text{ hr}}{1 \times 1}$$

$$= 135 \text{ mg 8 hourly}$$

Therefore, a maintenance dose of PO Theophylline immediate-release 125 mg every 8 hourly can be given for this patient.

Alternatively, changing the salt factor to 0.8 for Aminophylline will yield a maintenance dose of IV Aminophylline 507 mg/day, which can be given as 160 mg 8-hourly dosing or as continuous infusion of 21 mg/hr.

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Clinical Pharmacokinetics Pharmacy Handbook
Second Edition

VALPROIC ACID

Valproic Acid is an agent that is chemically related to free fatty acids and is used in the treatment of generalized, partial and absence (petit mal) seizures. As such, it has the widest spectrum of activity compared to other currently available antiepileptic drugs.[2] The Standard and New Antiepileptic Drugs (SANAD) trial stated that valproic acid is recommended as first line choice in treating focal or generalized seizures compared to lamotrigine and topiramate.[11]

In addition, valproic acid is used to prevent migraines and treat a variety of psychiatric disorders such as mania associated with bipolar disorder, anxiety, depression, psychosis, substance-abuse withdrawal and other behavioural disturbances.[2]

The precise mechanism of action is uncertain; its antiepileptic effect is thought to result from its ability to either increase concentrations of the neuroinhibitor γ-aminobutyric acid (GABA), potentiate the postsynaptic response to GABA, or to exert a direct effect on cellular membranes.[3]

KEY PARAMETERS:

Therapeutic Range	Seizures: 50 – 100 mg/L[1,3,4] Psychiatric Disorder: 50 – 125 mg/L [1,2,4]
Bioavailability (F)	Intravenous: 100%[1] Oral: 100%[1] Sustained Release Tablet: 90% [1] Extended Release Tablet: 80 – 90% [1]
Salt Factor (S)	1.0 [1,2]
Volume of Distribution (Vd)	Pediatric: 0. 22 (± 0.05) L/kg [2] Adults: 0.15 (± 0.10) L/kg [2]

Clearance (CL)	**Pediatric** Monotherapy: 10 – 20 ml/kg/hr[3] Polytherapy: 20 – 30 ml/kg/hr[3] **Adult** Monotherapy: 7 – 12 ml/kg/hr[3] Polytherapy: 15 – 18 ml/kg/hr[3]
Half-life ($t_{1/2}$)	**Pediatric** Monotherapy: 6 – 8 hours[3] Polytherapy: 4 – 6 hours[3] **Adult** Monotherapy: 12 – 18 hours[3] Polytherapy: 4 – 12 hours[3]

PHARMACOKINETIC

Bioavailability (F)

Valproic acid is completely absorbed with bioavailability (F) and salt forms (S) equivalent 1.0 for the intravenous, oral solution and capsules. The bioavailability of enteric-coated tablets is similar to capsule as the tablet is not sustained in their release but the drug absorption is delayed after ingestion. [1,3]

The bioavailability of extended release tablet is between 80% - 90%. It has a more sustained plasma profile comparable to continuous infusion model. The bioavailability of sustained release tablet is 90%.[1]

Volume of Distribution (Vd)

Valproic acid is highly bound to serum albumin with typical values of 90 – 95%.[1, 2, 3] Binding of valproic acid to serum albumin will become saturated within the therapeutic range (or when valproic acid concentration exceeds 50 mg/L).[1,3] This concentration dependent protein binding of valproic acid causes the drug to follow nonlinear pharmacokinetics (less protein binding and higher unbound fraction of drug at higher concentrations).[3]

The following table shows disease states and conditions that alter valproic acid plasma protein binding.

Hypoalbuminaemia [3] **(Albumin level below 30 g/L are associated with high valproic acid unbound fraction/free drug in the plasma) [3]**	• Liver disease • Nephrotic syndrome • Pregnancy • Cystic fibrosis • Burns • Trauma • Malnourishment • Elderly
Displacement by endogenous substances [3]	• Hyperbilirubinaemia (> 2 mg/ml) • Jaundice • ESRF (CrCl <10 – 15 ml/min) with uremia (BUN >80 – 100 mg/dL)
Displacement by exogenous substances [3]	• Drugs that are highly bound to albumin (warfarin, phenytoin, aspirin >2 g/day and some highly bound NSAID)

*Vd of valproic acid in these clinical conditions may be larger because of reduced plasma protein binding. [3]

Metabolism

Valproic acid metabolism is enhanced by other drugs that can induce hepatic enzymes activity [1]. One of the metabolite (4-en-valproic acid) may be associated with the drug's propensity to cause hepatotoxicity. [3]

Clearance (CL)

Valproic acid is almost entirely eliminated through hepatic metabolism (>95 %) and less than 5 % is eliminated by the renal route. [1]

	Monotherapy[3]	Polytherapy[3]
Pediatric	10 – 20 ml/kg/hr	20 -30 ml/kg/hr
Adult	7 – 12 ml/kg/hr	15 -18 ml/kg/hr

*Clearance of valproic acid may correlate better with ideal body weight rather than total body weight in obese patient [2,3]

*Liver dysfunction (Liver Cirrhosis, Acute Hepatitis) have reduce valproic acid clearance (Cl: 3 – 4 ml/kg/hr) due to reduced amount of enzymes as a result of destruction of liver parenchyma. [3,4]

Half-life ($t^{1}/_{2}$)

	Monotherapy	Polytherapy
Pediatric	6 – 8 hours [3]	4 – 6 hours [3]
Adult	12 – 18 hours [3]	4 -12 hours [3]

*Average half life for valproic acid in patients with liver disease is 25 hours.

Time to Peak[1]

- Oral: 1 to 3 hours (before meal)
- Oral: 6 to 8 hours (after meal)
- Intravenous: at the end of 1 hour infusion

Indication and Therapeutic Range

Indication	Therapeutic Range at Steady State
Generalized, partial and absence seizures (petit mal)[3]	50 – 100 mg/L [1,3,4]
Mania with bipolar disorder[3], anxiety, depression, psychosis, substance-abuse withdrawal and other behavioural disturbances [1]	50 – 125 mg/L [1,2,4]

* Valproic acid concentrations exceeding 100 mg/L are often required in patients with partial seizure [1]
* IV Valproate is not recommended for post-traumatic seizure prophylaxis in patients with acute head trauma due to increased mortality compared to IV Phenytoin [4]
* Valproate acid should be withdrawn gradually to minimize the potential of increased seizure frequency

  (Unless safety concern requires a more rapid withdrawal) [4]

DOSAGE

<table>
<tr><td>Pediatric</td><td>
For generalized or partial seizure
Initially: 5 mg/kg for 8 to12 hourly [5]
<table>
<tr><th>Monotherapy</th><th>Polytherapy</th></tr>
<tr><td>10 mg/kg/day [3]</td><td>20 mg/kg/day [3]</td></tr>
</table>
Increase dose if required to max 20 mg/kg for 8 to12 hourly [5]

For status epilepticus[10]
20 mg/kg (max loading 1.25 g, given over 1-5 minutes at 20-50 mg/min)
Then, infusion 1-5 mg/kg/hour for 6-12 hours.
</td></tr>
</table>

<table>
<tr><td rowspan="3">Adult</td><td>

For generalized or partial seizure

Loading Dose: 20 – 25 mg/kg[2]

Maintenance: 15 mg/kg/day up to 60 mg/kg/day [1]

<table>
<tr><th>Monotherapy</th><th>Polytherapy</th></tr>
<tr><td>7.5 mg/kg/day [3]</td><td>15 mg/kg/day [3]</td></tr>
</table>

Dose adjustment 5 – 10 mg/kg/day at weekly intervals [4]

For status epilepticus[11]

15-20 mg/kg slow bolus (infuse over ½ hours), followed by 1mg/kg/hour for 6 hours.

</td></tr>
<tr><td>

For psychiatric disorders

25 mg/kg/day up to 60 mg/kg/day [1]

</td></tr>
<tr><td>

For migraines

500 mg OD for 7 days followed by 1000 mg daily thereafter [1]

</td></tr>
</table>

Note: Dose based on Ideal Body Weight for obese patient [3]

Renal Impairment

No dosage adjustment necessary but renal function needs to be monitored closely. High urea level can displace valproic acid from binding site (decreased protein binding) and unbound valproic acid will be higher in this clinical condition. [3,4]

Valproic acid is not removed efficiently by haemodialysis. [2,3]

Hepatic Impairment

Valproic acid has been associated with hepatic damage and patients with existing liver disease should be classified according to liver dysfunction index (Child-Pugh score) before initiation of the drug. [3]

Test/ Symptom	Score 1 point	Score 2 points	Score 3 points
Total Bilirubin (mg/dL)	<2.0	2.0 – 3.0	>3.0
Serum Albumin (g/L)	>35	28 – 35	<28
Prothrombin time, prolongation (secs)	<4	4 – 6	>6
Ascites	Absent	Mild	Moderate
Hepatic Encephalopathy	None	Moderate	Severe

*Child-Pugh score for patients with liver disease

- A Child–Pugh score greater than 8 is grounds for a decrease of 25 – 50% in the initial daily drug dose for valproic acid. [3]
- Severe impairment: contraindicated [4]

INTERACTION

Valproic Acid is an enzyme inhibitor and is subject to enzyme induction [2]

Valproic Acid may increase concentration/effects of the following drugs	The concentration /effects of Valproic Acid may be increased by	The concentration /effects of Valproic Acid may be decreased by
Amitriptyline[3] Carbamazepine Epoxide (by inhibition of epoxide prolase) [2,3] Clonazepam[3] Ethosuximide [2,3] Lamotrigine [2,3] Lorazepam [2] Nortriptyline[3] Phenobarbital [1,2] Phenytoin [1,2,3] Primidone[3,4] Risperidone[4] Zidovudine[3]	Cimetidine [3] Chlorpromazine [3] Felbamate [3] Topiramate [4]	Carbamazepine [1,2,3] Carbapenem [4] Lamotrigine[3] Phenytoin [1, 2, 3] Phenobarbitone [1, 2] Primidone [2] Rifampicin [2]

SAMPLING

Steady State: 2 to 4 days [1]

Sampling time:

Oral / Intravenous maintenance dose: 30 minutes OR just before next dose.[1]

Monitoring is recommended in the following conditions:

- Initiation of therapy
- Change in dosing regimen
- Addition of other antiepileptic drugs to the patient's regimen
- Change in patient's clinical course (decrease in seizure control or laboratory/physical finding consistent with valproic acid toxicity)
- Any claims/complains of valproic acid side effects

MONITORING PARAMETER

- Liver enzymes (at baseline and frequently during therapy especially during the first 6 months)[4]
- Full blood count with platelets (baseline and periodic intervals)[4]
- Serum ammonia (with symptoms of lethargy, mental status change)[4]
- Body weight
- Blood pressure
- Heart rate

ADVERSE DRUG REACTION

Side effects[1,3]	• Alopecia • Abdominal cramps • Diarrhoea • Nausea • Pancreatitis • Hyperammonemic encephalopathy • Hepatotoxicity • Weight gain • Vomiting
Patients at higher risk of hepatotoxicity [1]	• Young patient (hepatic failure resulting in fatalities has occurred in patient <2 years of age)[4] • Patient with developmental delay • Metabolic disorders • Patient receiving anticonvulsant combination therapy

Some concentration related side effects:

Concentration	Side effects
When serum concentration (>75 mg/L) [3]	Tiredness, lethargy, sedation and ataxia
When serum concentration (>100 mg/L)[3]	Tremor
When serum concentration (>110 mg/L for female, >135 mg/L for male) [4]	Probability of thrombocytopenia
When serum concentration (>175 mg/L) [2,3]	CNS toxicity, coma and stupor

*Sedation and drowsiness can be due to interaction between valproic acid and other concomitant anticonvulsant therapy [1]

*Pharmacodynamic interaction between valproic acid and lamotrigine may lead to an increased incidence of tremor and rash [2]

*It was reported that a four fold increase in congenital malformations happen during the first trimester of pregnancy [4]

Overdosage/Toxicology:

Patients with mild to moderate toxicity of valproic acid generally presented with CNS depression such as lethargy, sedation, vomiting and tachycardia. In severe toxicity, patients typically develop more severe CNS depression such as coma, myotic pupils, tachycardia, hypotension, QT prolongation, and respiratory depression. [9]

Management of Overdosage/Toxicology:

1) Mild to moderate toxicity: [9]

- **Activated charcoal** may be considered if the ingestion is recent. Repeat valproic acid concentrations every 4-6 hours and consider multiple dose activated charcoal if the level is increasing.

2) Severe toxicity: [9]

- Antidote: **L-carnitine**

Indication: Valproic acid-induced coma, hyperammonemia, hepatotoxicity, concentration of valproic acid >450 mg/L.

Dose: IV L-carnitine 100 mg/kg over 30 minutes (maximum 6 g) followed by 15 mg/kg every 4 hours until clinical improvement.

- **Naloxone** may be considered in patients with CNS depression, valproic acid-induced coma and/ or significant respiratory depression.
- **Haemodialysis/haemoperfusion** is reserved for patients who are not responding to supportive care, especially with concomitant severe metabolic disturbance and/ or a serum valproic acid concentration >1000 mg/L.

*Monitor valproic acid concentrations every 4 – 6 hours until the concentrations are clearly declining and symptoms have resolved. [9]

DILUTION AND ADMINISTRATION

Dilution of drug	Reconstitute with 3.8 ml WFI (provided) to give 100 mg/ml (if 4 ml WFI solvent is used, the final concentration will become 95 mg/ml)[6] Can be further diluted in 50 – 100 ml of NS/D5W for infusion [6]

- Stable for 24 hours at room temperature [1]
- Each vial is for single dose injection only. Any unused portion should be discarded [6]

Drug administration	Infusion Rate
Rapid infusion[3]	5 – 10 minutes (≤45 mg/kg)
IV intermediate infusion [3]	60 minutes (≤20 mg/min)

CALCULATION [1]

A) Dose Initiation

1. Calculate clearance (CL):

$$\text{CL (L/hr)} = \frac{\text{CL (ml/kg/hr)} \times \text{BW(kg)}}{1000 \text{ ml}}$$

2. Calculate volume of distribution (Vd):

$$\text{Vd (L)} = \text{Vd (L/kg)} \times \text{BW (kg)}$$

3. Calculate elimination rate constant (K_e):

$$\text{Ke (hr}^{-1}) = \frac{\text{CL (L/hr)}}{\text{Vd (L)}}$$

4. Calculate half life (t ½):

$$\text{t½ (hr)} = \frac{0.693}{\text{Ke } (hr^{-1})}$$

To initiate loading dose

*Recommended loading dose is 20 – 25 mg/kg [2]

$$\text{LD (mg)} = \frac{\text{Css desired (mg/L)} \times \text{Vd (L)}}{\text{S} \times \text{F}}$$

To initiate maintenance dose

$$\text{MD (mg)} = \frac{\text{CL (L/hr)} \times \text{Css desired (mg/L)} \times \text{Interval (hour)}}{\text{S} \times \text{F}}$$

B) Dose Adjustment

1. Estimate clearance (CL) from the obtained concentration

$$\text{Cl (L/hr)} = \frac{\text{S} \times \text{F} \times \text{Dose (mg)}}{\text{Css measured (mg/L)} \times \text{Interval (hour)}}$$

2. Determine Css target and calculate new maintenance dose

$$\text{MD (mg)} = \frac{\text{Cl (L/hr)} \times \text{Css target (mg/L)} \times \text{Interval (hour)}}{\text{S} \times \text{F}}$$

RESULT EVALUATION

CONCENTRATION	CONTRIBUTING FACTOR	RESPONSE	RECOMMENDATION
Subtherapeutic **< 50 mg/L**	• **Compliance** • **Wrong sampling time** • **Insufficient dose** • **Drug interaction** • **Hypoalbuminemia** • **Renal failure**	**Poor** **Good**	**If compliance & sampling time is satisfactory, increase the dose appropriately & resample. For patient in ward, oral dose can be converted to IV dosing** **Continue current dose**
Within Normal Therapeutic Range 50 – 100 mg/L		**Poor** **Good**	**If compliance & sampling time is satisfactory, increase the dose (not more than maximum recommended dose)** **Continue current dose**
Potential toxic/ Toxic **> 120 mg/L**	• **Overdosage** • **Underlying disease/ factors** • **Possible drug interaction**	**Toxic effect:** • **Deep sleep** • **Coma** • **Confusion** • **Hyponatremia** • **Ataxia** • **Arrhythmia** • **Leukopenia**	**Withhold treatment, monitor level and treat signs & symptoms of toxicity (if required), then adjust dose accordingly**

The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic – pharmacodynamic parameter and clinical condition should be considered before making any recommendations.

CASE DISCUSSION

Case 1:

KL is a 51-years-old, 60 kg male with tonic-clonic seizures who requires therapy with oral valproic acid. He has normal liver function and takes no medications that induce hepatic enzymes. Suggest an initial valproic acid dosage regimen designed to achieve a steady-state valproic acid concentration equal to 50 mg/L.

The clearance rate for an adult patient not taking other drugs that induce hepatic drug metabolism is 7–12 mL/kg/h. Using a value of 10 mL/kg/h:

$$\text{CL (L/hr)} = \frac{10\ (\text{ml/kg/hr}) \times 60(\text{kg})}{1000\text{ml}}$$

= 0.60 L/hr

$$\text{Vd (L)} = 0.15\ (\text{L/kg}) \times 60\ (\text{kg})$$

= 9 L

$$\text{Ke (hr}^{-1}) = \frac{0.60(\text{L/hr})}{9\ (\text{L})}$$

= 0.067 h^{-1}

$$t½\ (\text{hr}) = \frac{0.693}{0.067\ (hr^{-1})}$$

= 10.34 hours

Oral Epillim 200 Enteric Coated tablets will be prescribed to this patient. (F=1)

$$\text{MD (mg)} = \frac{0.60\ (\text{L/hr}) \times 50\ (\text{mg/L}) \times\ 12\ (\text{hour})}{1\ \times\ 1}$$

= 360 mg

~ rounded to 400 mg 12 hourly

Steady-state trough valproic acid serum concentration should be measured after steady state is attained in 3–5 half-lives. Since the patient is expected to have a half-life equal to 10 hours, the valproic acid steady-state concentration could be obtained any time after the second day of dosing (5 half-lives = 50 hours). Valproic acid serum concentrations should also be measured if the patient experiences a worsening of seizure control, or if the patient develops potential signs or symptoms of valproic acid toxicity.

Case 2:

HU is a 25 years old, 85 kg male with tonic-clonic seizures who requires therapy with intravenous valproic acid. He has normal liver function and takes no medications that induce hepatic enzymes. Suggest an initial valproic acid dosage regimen designed to achieve a steady state valproic acid concentration equal to 75 mg/L.

The clearance rate for an adult patient not taking other drugs that induce hepatic drug metabolism is 7–12 mL/kg/h. Using a value of 10 mL/kg/h:

$$\text{CL (L/hr)} = \frac{10\ (\text{ml/kg/hr}) \times 85(\text{kg})}{1000\text{ml}}$$

= 0.85 L/hr

$$\text{Vd (L)} = 0.15\ (\text{L/kg}) \times 85\ (\text{kg})$$

= 13 L

$$\text{Ke (hr}^{-1}) = \frac{0.60(\text{L/hr})}{13\ (\text{L})}$$

= 0.046 h^{-1}

$$t½\ (\text{hr}) = \frac{0.693}{0.046\ (hr^{-1})}$$

= 15 hours

Valproic Acid injection will be prescribed to this patient (F = 1).

$$\text{MD (mg)} = \frac{0.85\ (\text{L/hr}) \times 75\ (\text{mg/L}) \times\ 12\ (\text{hour})}{1\ \times\ 1}$$

= 765 mg

~ 800 mg 12 hourly

For loading dose:

$$\text{LD (mg)} = \frac{75\ (\text{mg/L})\ \times\ 13\ (\text{L})}{1\ \times\ 1}$$

= 975 mg

~ 1000 mg (Intravenous doses should be given over 1 hour (<20 mg/minute).

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Clinical Pharmacokinetics Pharmacy Handbook
Second Edition

VANCOMYCIN

It is recommended as a treatment for complicated skin infections, bloodstream infections, endocarditis, bone and joint infections, gastrointestinal and central nervous system infection caused by:

Selective Gram positive organisms:

1. Methicillin resistant *Staphylococci* and *Streptococci*
2. *Enterococci*
3. *Rhodococci*
4. *Clostridium*

Inherently resistant organisms:

1. Few species of *Enterococci*
2. *Lactobacillus*
3. *Leuconostoc*
4. *Pediococcus*
5. *Erysipelothrix spp*

KEY PARAMETERS:

Therapeutic Range	Refer to 'Indication and Therapeutic Range' section
Bioavailability (F)	Oral : < 5% [1] IV : 100 % [1]
Elimination Rate (Ke)	Ke (hr^{-1}) = 0.0044 + (CrCL x 0.00083) [3]
Volume of Distribution (Vd)	Vd (L)= 0.7L/kg
Clearance (CL)	Cl = 0.695 (CrCL, mL/min) + 0.05 [7]
Half-life ($t_{1/2}$)	Adult: 5 – 11 hours [4] Children: 2– 3 hours [4]

PHARMACOKINETIC

Bioavailability (F): [1]

Oral: < 5%

Intravenous: 100%

Volume of Distribution (Vd):

The average Vd for vancomycin in non-obese adults with normal renal function is 0.7 L/kg. However, it can be calculated using these equations:

Vd (L)= 0.17 (age) + 0.22 (TBW) + 15 [2]

or

Vd (L)= (0.5 – 1) L/kg X BW (kg) [2]

Clearance (Cl):

Cl = 0.695 (CrCL, mL/min) + 0.05 [7]

In healthy subject, 30% of the systemic vancomycin clearance is by non-renal mechanism and the non-renal clearance is concentration dependent. Assuming protein binding to be between 10% and 20%, renal vancomycin excretion is predominantly by glomerular filtration. [13]

Clearance can also be calculated using:

Cl = Vd/Ke (L/hr)

Half-life ($t_{½}$):

Neonates	6 – 10 hours [4]
Children	2 – 3 hours [4]
Adult	5 - 11 hours [4]
Adult, renal failure	120-140 hours [7]
Adult, obese	3-4 hours [7]
Burn patient	4 hours [1]

Indication and Therapeutic Range:

Vancomycin is used to treat severe gram positive infections. It exhibits time-dependent antibiotic. Thus, trough concentration combined with AUC_{24} estimation are the practical method for monitoring vancomycin effectiveness. AUC_{24} > 400 shows an optimal antibiotic exposure in ensuring the treatment efficacy, and a capping maximum limit in AUC_{24} of 600 signifies the treatment safety with vancomycin.

Trough:

General: 10 – 15 mg /L [5]

- The target trough level will depend on the ability to achieve AUC_{24} of 400-600 for optimal antibiotic exposure [20]
- For a pathogen with an MIC of 1 mg/L, the minimum trough concentration would have to be at least 15 mg /L to generate the target AUC_{24}/MIC of 400. [5]

For continuous infusion:

Conventional target: 15- 25 mg /L [16,17]

Critically ill and severe infection: 20-30 mg /L [16,25]

Conversion Factor: mg /L (~mg /L) x 0.69 = µmol/L

Pharmacodynamic Targets: goal AUC and Trough [20, 26]

Indication	Target Index
Most Indications	
Bacteremia (all sources, including SSTI) Endocarditis Bone/joint infection Necrotizing fasciitis Pneumonia Empiric therapy for neutropenic fever Sepsis, source unknown	Target AUC_{24} 400-600, with trough 10-20 mg/L **(AUC_{24} is primary target)**
Meningitis (Empirical or definitive), CNS infection MRSA infections with MIC = 2	
AUC_{24}-based protocol Trough-based protocol	600-800 15-20 mg /L

Renally impaired patients (AKI, CKD)	
AUC_{24}-based protocol Trough-based protocol	400-600 15-20 mg/L
• In general, goal AUC_{24} 400-600 for *S.aureus* • Monitor closely with trough > 15 or AUC > 700: increased risk of nephrotoxicity • Vancomycin may be continued in clinically responding patients with MRSA with vancomycin MIC = 2	

DOSAGE

Pediatric:

Age	Dose
Neonate less than 29 weeks postmenstrual age	15 mg/kg OD [14]
29-35 weeks postmenstrual age	15 mg/kg BD [14]
Over 35 weeks postmenstrual age	15 mg/kg TDS[14]
Infant >1 month & children	10 -15 mg/kg every 6 h [4]

Adult:

Loading dose [5, 19, 26]

All patients initiated on vancomycin should be assessed to determine whether a LD is likely to improve outcomes. The two key components involved in making this determination include **indication for vancomycin** and **severity of illness**. The criteria below are meant to aid the clinician in making this determination. [26]

Patients meeting either criterion A or B should receive a vancomycin LD:	
A	Meeting **≥2** of the following (all indications except non-necrotizing fasciitis or bacteremic SSTI, UTI, or prophylaxis post-surgery): • Temperature > 38°C or < 36°C • Heart rate > 90 beats per minute • Respiratory rate > 20 breaths per minute • WBC > 12,000/mm3, < 4,000/mm3, or > 10% bands • Hypotension (systolic blood pressure < 90 mmHg, MAP < 60 mmHg, or requiring vasopressors)
B	Treatment of meningitis/CNS infection (suspected or documented)

In rare instances when such information cannot be obtained without a significant delay in treatment, it is reasonable to give a LD.

Recommendation for loading dose based on population:

LOADING DOSE	
Population	**Loading Dose (mg)**
CrCl > 30 mL/min and stable or improving	Weight-based: 25-30 mg/kg TBW*
CrCl ≤ 30 mL/min or declining, not on dialysis	Weight-based: 20 mg/kg TBW*
Intermittent Hemodialysis (IHD)	Weight-based: 20 mg/kg TBW*
Continuous Renal Replacement Therapy (CRRT)	Weight-based: 20 mg/kg TBW*
Peritoneal Dialysis (PD)	Intraperitoneally: 2 gram*
	Weight-based: 20 mg/kg TBW IV*

* (ASHP, Stanford)
Use total body weight (TBW) if TBW < IBW (ASHP, Stanford)
Use ideal body weight (IBW) for non-obese patients
Use adjusted body weight (ABW) for obese patients [total body weight (TBW) >20% of IBW or BMI >30 kg/m2]

Conventional Dosing: [4, 5, 18, 19, 23, 26]

MAINTENANCE DOSE						
BW(kg) / [a]CrCl (ml/min)	**>90**	**75-89**	**60-74**	**50-59**	**30-49**	**Sampling Time**
>60	1000 mg tds	750 mg tds	1000 mg bd	750 mg bd	500 mg bd	Pre level on 3rd dose
40-59	750 mg bd	750 mg bd	500 mg bd	750 mg od	500 mg od	
20-39	750 mg od	750 mg od	500 mg od	500 mg od	500 mg od	

<20 HD	ESRF: Initial dose: Give loading dose as chart (a) then sample blood for monitoring 24 hours after dose. [c](Re-dose 15-20 mg/kg when plasma concentration <20 mg/L and depending on the residual renal function)	Random level: • 24 hours after 1st dose. • 48 hours after subsequ-ent dose (pre HD preferred)
CAPD	ESRF: Initial dose: Give loading dose as chart (a) then sample blood for monitoring 24 hours after dose. (Re-dosing depends on the type of dosing (intermittent or continuous) and serum trough vancomycin concentration*) *Serum trough vancomycin concentration is advised to be kept between 15-20 mg/L	
[b]Dilution & Infusion Guide	• 500 mg/ 100cc NS/ 1hour • 750-1000 mg/ 200cc NS/ 2 hours • 1000-2000 mg/ 400cc NS/3 hours	

[a]Use Cockroft Gault formula. Not valid for SCr <60 umol/L and elderly >65 years of age. Get consultation from CPS pharmacist.
[b]Do not exceed 10 mg/min to avoid red man syndrome discomfort, hypotension, cardiac arrest.
[c]Subsequent doses to be recommended by CPS pharmacist.

Continuous Infusion [9]:

LOADING DOSE	
< 40 kg	500 mg IV in 100 mL 0.9% sodium chloride or 5% glucose over 1 hour
< 70 kg	1 g IV in 250 mL 0.9% sodium chloride or 5% glucose over 2 hours
≥ 70 kg	1.5 g IV in 250 mL 0.9% sodium chloride or 5% glucose over 2.5 hours

Central administration: the final concentration should not exceed 10 mg/mL
Peripheral administration: the final concentration should not exceed 5 mg/mL

Start the maintenance of IV infusion immediately after the loading dose. The dose depends on the patient's renal function. Infusions should be administered in 250 mL 0.9% sodium chloride or 5% glucose over 12 hours. The total daily dose should be split into two and the infusion rate set at 20.8 mL/hr.

MAINTENANCE DOSE		
Creatinine Clearance (mL/min)	**Daily maintenance dose**	**Dose in each 250 mL infusion bag for administration over 12 hours**
<20	500 mg	250 mg
20-34	750 mg	375 mg
35-59	1000 mg	500 mg
60-79	1500 mg	750 mg
80-99	2000 mg	1000 mg
>100	2500 mg	1250 mg

For dosage adjustments in continuous infusion [16, 19, 26]

Vancomycin Concentration	Suggested dosage change
< 15 mg/L	Increase the daily dose by 500 mg
15 – 25 mg/L	No change
> 25 mg/L	Decrease the dose by 500 mg*
> 30 mg/L	Stop the infusion and recheck serum concentration next morning. Restart at a lower dose

*If the patient is only receiving 500 mg/day, reduce the dose to 250 mg/day

Renal Impairment: [4, 18, 23]

CrCL (mL/min)	Dosage Adjustment
> 50	15 – 20 mg/kg/dose every 12 hours (usual : 750 – 1500 mg)
20 – 49	15 – 20 mg/kg/dose every 24 hours (usual : 750 – 1500 mg)
< 20	Need longer intervals, re-dosing determined by serum concentration monitoring

Dialysis (D)

Conventional: poorly dialyzable (0 – 5%) [4]

High-flux membranes & CRRT: increase vancomycin clearance & requires dosing replacement [4]

Type of Dialysis	Dosage
Haemodialysis (HD)[4]	Following loading dose of 15-20 mg/kg, given 500 mg to 1000 mg after each dialysis session. Pre dosing based on pre-HD level*: <10 mg/L: administer 1000 mg after HD 10 – 25 mg/L: administer 500-750 mg after HD >25 mg/L: Hold vancomycin *based on clinical judgement
CAPD[9,18]	**Intermittent dose** (once/day): 15 – 30 mg/kg every 5 – 7 days **Continuous dose** (per/L exchange): Loading : 30 mg/kg Maintenance : 25 mg/L OR 1.5 mg/kg/bag
CVVH[4]	Following loading dose of 15 – 20 mg/kg, give 1g every 48 hours
CVVHD / CVVHDF	Following loading dose of 15 – 20 mg/kg, give 1g every 24 hours

INTERACTION

Drug-drug interaction:

Increase effect/toxicity	Vancomycin may increase the concentrations/effects of: aminoglycosides, colisthimethate, gallium nitrate and neuromuscular-blocking agent [4]
Decreased drug concentration/effects	Vancomycin may decrease the concentrations/effects of thyphoid vaccine and BCG vaccine [4]

Drug- disease interaction:

Burn	Increase vancomycin CL, require more frequent dose [1]
Hepatic insufficiency	Reduce degree of vancomycin protein binding (20%), require higher than normal dose (>30 mg/kg/day in adult) [1]
Renal failure	Vancomycin total clearance decrease proportionally to decrease in CrCL[7]
Obesity	Increase vancomycin clearance, Vd dose not changes significantly with obesity and is best dosed with IBW for patient who are >30% overweight [7]

SAMPLING

Time to monitor serum concentration (at steady state):

Monitoring of both trough and peak concentrations is highly recommended as the first step in estimating patient's specific parameters (Ke and Vd) and AUC_{24}.

When to obtain serum vancomycin concentration (after dose initiation or adjustment):

Normal renal function: After 3rd dose or after 4-5 half lives [3, 5, 8]

Impaired renal function: After 24 hours

Intermittent dose:

Trough: just before next dose [4]

Peak: 1 hour after end of infusion [4]

Stat dose (unstable renal function):

Random depending on the serum concentration [4] or trough monitoring [8]

Continuous Infusion:

Take a sample after 12 – 24 hours of starting the continuous infusion then every 1 - 2 days, or daily if the patient has unstable renal function. [16]

MONITORING PARAMETER

i) Culture & sensitivity [7,8]
   a. Organism susceptibility towards vancomycin
   b. Clearance of bacteremia
ii) White blood cell count [4,7]
iii) Renal function [4,7,20]
   a. Serum creatinine incremental by 26.5 mcmol/L (AKI detection)
iv) Albumin concentration [27]
v) Symptomatic improvement [7,8]
   a. Vital signs (Temperature, heart rate, blood pressure)
   b. Hemodynamic stability
   c. GCS and alertness level
vi) Audiogram [4]

ADVERSE DRUG REACTION

Parenteral (4):

>10 % :	1 – 10 % :	<1%
CVS : hypotension accompanied by flushing	CNS : Chills, drug fever	Otoxicity, renal failure, thrombocytopenia, vasculitis
Dermatologic : Red man syndrome	Hematologic : Eosinophilia, reversible neutropenia	-

DILUTION AND ADMINISTRATION

Dilution of drug	Diluent: normal saline or D5W [4]. Reconstitute vials with 20 mL of SWFI for each 1 g of vancomycin (500mg/10mL). The reconstituted solution must be further diluted with at least 100 mL of compatible diluents per 500 mg of vancomycin prior to parenteral administration [4]. Maximum concentration : not to exceed 5 mg/mL[4] For fluid restriction patient, maximum concentration: 10 mg/mL[8] Stability: Reconstituted – room temperature or under refrigeration for 14 days [4] Diluted - under refrigeration for 14 days or at room temperature for 7 days [4]

Drug administration:

Infusion over at least 60 minutes [4,8] or a maximum infusion rates of 10 mg/min, whichever is longer [8]

CALCULATION

Trough & Peak level available [2]

a) $Ke = \frac{\ln Cpost - \ln Cpre}{T - (t2 - t1)}$

b) $t½ = \frac{0.693}{Ke}$

c) $Cmax = Cpost \times e^{ket'}$

d) $Cmin = Cmax \times e^{-KeT}$

e) $Vd = \frac{Dose\ (mg)}{BW \times Cmax(1-e^{-KeT})}$

f) $Expected\ Cmax = \frac{New\ Dose\ (mg)}{Vd \times BW(1-e^{-KeT})}$

g) $Expected\ Cmin = Expected\ Cmax \times e^{-KeT}$

Ke	Elimination rate constant (h-1)
T	Dosing interval (h)
t1	Pre sampling time
t2	Post sampling time
t½	Half life (h)
Cmin	Min conc. (mg/L)
Cmax	Max conc. (mg/L)
t′	Interval between end of infusion and post sampling time
Vd	Volume of distribution (L/kg)
BW	Body weight (kg)

Only trough level available [2]

a) $Cmax = Cmin + \frac{Dose\ (mg)}{V\ (L)}$

b) $Ke = \frac{\ln Cmax - \ln Cmin}{T}$

c) $t½ = \frac{0.693}{Ke}$

d) $New\ dose = \frac{Cmin\ target \times V(L) \times (1-e^{-KeT})}{e^{-KeT}}$

e) $Expected\ Cmax = \frac{S \times F \times New\ dose(mg)}{V(L) \times (1-e^{-KeT})}$

f) $Expected\ Cmin = Expected\ Cmax \times e^{-KeT}$

Cmin	Cpre (mg/L)
Cmax	Max conc. (mg/L)
S	1
F	1
V	(>18 years old) 0.17 (age) + 0.22 (TBW in kg) + 15
V	(< 18 years old) (0.5 – 1) L/kg X BW (kg)
Ke	elimination rate constant (h-1)
T	Dosing interval (h)
t½	half life (h)

Area Under the Curve 24 hours

4 methods:

- $\text{AUC } 24 = (24 \times \text{Cmin}) + \left[(0.5 \times \text{T})(\text{Cmax} - \text{Cmin})\left(\frac{24}{\text{T}}\right)\right](0.33)$

- $\frac{\text{AUC } 24}{\text{MIC}} = \frac{\text{Vancomycin total daily dose}}{\text{Cl (L/hr)} \times \text{MIC (mg/L)}}$

AUC_{24}	mg.h/L
CrCL	mL/min
Dose	Mg
Co	Conc. at start of infusion Co = Cmax X $e^{Ke\,(t'')}$
t''	Interval between start of infusion and post sampling time
t`	Infusion time
inf	Infusion phase
elim	Elimination phase

Log Method

- $\text{AUC} = \frac{\text{Co} - \text{Cmin}}{\text{Ke}}$

$\text{AUC } 24 = \text{AUC x dosing frequency}$

Linear-log / Trapezoidal method

- $\text{AUC(inf)} = \text{t` x } \frac{\text{Cmin} + \text{Cmax}}{2}$

$\text{AUC(elim)} = \frac{\text{Cmax} - \text{Cmin}}{Ke}$

$\text{AUC } 24 = (\text{AUC}inf + \text{AUC}elim) \text{ X } \frac{24}{\text{T}}$

- $\text{New TDD} = \text{Current TDD x } \frac{\text{AUC desired}}{\text{AUC Calculated}}$

*TDD: Total Daily Dose

RESULT EVALUATION

CONCENTRATION	RESPONSE	CONTRIBUTING FACTOR	RECOMMENDATION
Subtherapeutic	**Poor**	• **Fluid overload** • **Ascites** • **Wrong sampling time** • **Insufficient dose** • **Drug interaction** • **Burn**	➢ **Correct the fluid imbalance (if fluid overload), increase the dose appropriately & resample** ➢ **Repeat another sample for confirmation** ➢ **Increase the dose appropriately & resample** ➢ **Use alternative drug if possible, if unavoidable, increase the dose appropriately & resample** ➢ **Increase the dose appropriately (use conventional dosing) & resample**
	Good		**Continue current dose**
Within normal therapeutic range	**Poor**		**If sampling time is satisfactory & hydration status is fair, increase the dose (not more than max recommended)**
	Good		**Continue current dose**
Potential Toxic/ Toxic	**Toxic effect:** • **Nephro-toxicity** • **Ototoxic-ity** • **Red man syndrome** • **Neutro-penia**	• **Dehydration** • **Over dosage** • **Underlying disease/ factors** • **Renal failure** • **Possible drug interaction**	➢ **Withhold treatment (if necessary), hydrate the patient (if dehydrated) then reduce dose accordingly** ➢ **Withhold treatment then reduce dose accordingly** ➢ **Use alternative drug if possible, if unavoidable, withhold treatment (if necessary) then reduce dose accordingly**

The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Basic pharmacokinetic principles and patient's clinical condition should be considered before making any recommendations.

CASE DISCUSSION

A 19-years old Malay male with a body weight of 70 kg and height of 170 cm was hospitalized for 3rd degree burn with 39% total body surface area (TBSA). Past medical, social and medication histories are unremarkable and he was admitted to Burn ICU due to the burn complications that arisen afterwards.

He was initially started on IV Vancomycin 750 mg BD 4 days later based on the MRSA positive from his blood culture and sensitivity, and deterioration of condition despites of early treatment with IV Piperacillin-Tazobactam 4.5g QID. His serum creatinine was stable at 64 mcmol/L.

1. The first Vancomycin sampling taken on the fourth dose yields such results:

   Pre sampling @ 5.30am: 15.9 mg/L, dose given @ 6am over 1 hour

   Post sampling @ 8am: 29.3 mg/L

a) $Ke = \frac{\ln Cpost - \ln Cpre}{T - (t2 - t1)}$

$Ke = \frac{\ln 29.3 - \ln 15.9}{12 - (8 - 5.5)}$

$Ke = 0.0643 hr^{-1}$

b) $t1/2 = \frac{0.693}{Ke}$

$t1/2 = 10.78$ hours

c) $Cmax = Cpost \times e^{ket'}$

$Cmax = 29.3 \times e^{(0.0643)(1)}$

$Cmax = 31.25$ mg/L

d) $Cmin = Cmax \times e^{-KeT}$

$Cmin = 31.25 \times e^{-(0.0643)(12)}$

$Cmin = 14.44 mg/L$

e) $Co = Cmax \times e^{ket''}$

$Cmax = 31.25 \times e^{(0.0643)(2)}$

$Cmax = 35.53$ mg/L

f) $Vd = \frac{\text{Dose (mg)}}{Cmax(1-e^{-KeT})}$

$Vd = \frac{750\ (mg)}{33.32(1-e^{-(0.0643)(12)})}$

$Vd = 41.86\ L\ (0.59\ L/kg)$

g) $AUC = \frac{35.53-14.44}{0.0643}$

$AUC = 328$

h) $AUC\ 24 = 328 \times 2$

$AUC\ 24 = 656$

Since estimation of Cmin at steady state is within the range and the AUC_{24} achieved the target of 400-600, maintenance of the dose is suggested. Subsequent resampling of pre Vancomycin concentration was suggested to be conducted after five days of the first sampling for monitoring purpose.

2. The second sampling of pre Vancomycin concentration was withdrawn

Pre sampling @ 5.45am: 18.8 mg/L

a) $Cmax = Cpre + \frac{\text{Dose (mg)}}{Vd\ (L)}$

$Cmax = 18.8 + \frac{750mg}{41.86L}$

$Cmax = 36.72\ mg/L$

b) $Ke = \frac{\ln Cmax - \ln Cpre}{T}$

$Ke = \frac{\ln 36.72 - \ln 18.8}{12}$

$Ke = 0.0558\ hr^{-1}$

c) $t1/2 = \frac{0.693}{Ke}$

$t1/2 = 12.42$ hours

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