CLINICAL PHARMACOKINETICS SERVICE & ANTICOAGULATION GUIDELINES

Pharmacy Services
University of Kentucky HealthCare

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Disclaimer:

The ***Clinical Pharmacokinetics Service and Anticoagulation Guidelines*** are provided to assist with clinical pharmacokinetic monitoring and anticoagulation management of selected drugs for the **Department of Pharmacy Services at the University of Kentucky Chandler Medical Center**. Although the information contained in the guidelines has been obtained from reputable sources in accordance with currently available information, the editors do not assume any liability in connection with the use of any specific information contained herein. While great care has been taken to ensure the accuracy of the information presented, the reader is advised that it is possible that these pages contain some errors and omissions. If you find an error, please report it to Daniel Lewis at (859) 257-8403 or dalewi2@email.uky.edu.

The information provided in the guidelines is **not intended to replace sound clinical judgment** in the delivery of healthcare. Dosing of monitorable drugs and anticoagulation management require independent and informed decisions by appropriate healthcare professionals. Also, the information in this manual may not be applicable to other healthcare institutions. Complete information concerning drug administration, dosage, sampling times, clinical laboratory procedures, pharmacokinetic data, and pharmacological and toxic effects of monitorable drugs should be assessed and contrasted with other sources prior to its clinical use.

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UNIVERSITY OF KENTUCKY HOSPITAL
CHANDLER MEDICAL CENTER

POLICY NUMBER: PH-02-05
FIRST ISSUED: 1/88

Department of Pharmacy Policy

CURRENT AS OF: 05/07

SUBJECT: Clinical Pharmacokinetics Service Policy/Procedures

PURPOSE: To establish a standardized pharmacokinetic monitoring approach for patients receiving drugs that are routinely monitored utilizing serum drug concentrations at the University of Kentucky Hospital.

FUNCTIONS AFFECTED: Clinical Pharmacist Specialists, Clinical Staff Pharmacists, Pharmacy Residents, and Pharmacy Students

GENERAL: The Clinical Pharmacokinetics Service (CPS) Guidelines were developed to ensure safe and efficacious dosage regimens through the application of pharmacokinetic/pharmacodynamic principles and the determination of drug serum concentrations. The policy/procedure manual outlines standard guidelines which should be followed when providing clinical pharmacokinetic monitoring of the following drugs: aminoglycosides, carbamazepine, digoxin, fosphenytoin, lidocaine, lithium, phenobarbital, phenytoin (free and total), procainamide, quinidine, theophylline, valproic acid, and vancomycin. In addition to the above list, the CPS will also provide monitoring for warfarin for patients without assigned pharmacists.

Monitoring Responsibility

Within the pharmaceutical care process, the primary pharmacist/resident who attends rounds or precepts pharmacy students on the primary medical team is responsible for providing appropriate and cost-conscious therapeutic drug monitoring and provision of clinical pharmacokinetic evaluations. The CPS is responsible for overseeing the kinetic monitoring process for all patients and providing pharmacokinetic assessments for any patient that does not have an assigned primary pharmacist/resident. This responsibility is met through a team approach including a faculty member who serves as the Manager of Clinical Pharmacokinetics Service along with Pharmacy Practice Residents and PY4 pharmacy students as part of a resident/student rotation in Clinical Pharmacokinetics.

Patients with serum drug concentrations on non-covered services are identified on a daily basis utilizing Sunrise Clinical Manager (SCM). Also, the Therapeutic Drug Monitoring (TDM) Laboratory provides an electronic report of all completed serum drug concentrations of patients admitted to the hospital twice daily. This allows for identification of any non-covered patients who are prescribed monitorable drugs which have not obtained serum concentrations. Physicians may also initiate a request for pharmacy to provide a clinical pharmacokinetic evaluation by verbal communication or through a pharmacy to dose requisition in (SCM).

TDM Notification of Supratherapeutic Concentrations

The Therapeutic Drug Monitoring Laboratory is responsible for the analysis of all "routine" serum drug assays evaluated by pharmacy during a pharmacokinetic evaluation. The TDM Lab notifies the primary pharmacist of any supratherapeutic concentrations between 8AM-4PM during the week; after 4PM and on weekends and holidays the Pharm D. resident on-call (beeper #1875) is notified. The TDM Lab notifies the clinical pharmacokinetic service of any supratherapeutic levels for any uncovered service. All other TDM issues should be directed to either Daniel Lewis (pager #4331) or George Davis (pager #1740).

Documentation in the Patient Medical Record

When a patient has a serum drug concentration drawn, the primary pharmacist should write a "Clinical Pharmacokinetics" note in the patient's chart within 24 hours for normal or subtherapeutic concentrations. For concentrations that are supratherapeutic, the medical team should be notified immediately if clinically warranted and a chart note should be written as soon as possible, but no more than 12 hours after the concentration is reported. The chart note should contain all relevant patient information and pharmacokinetic parameters necessary to produce the dosing and monitoring recommendations. Please refer to the CPS Policy/Procedure Manual (http://www.hosp.uky.edu/pharmacy/cps/default.html) for guidelines for documentation of pharmacokinetic evaluations for specific monitorable drugs. Notes written by students and non-licensed pharmacists/residents must be co-signed by a Kentucky-licensed pharmacist within 24 hours.

Pharmacy to Dose Orders

Purpose:

To provide a policy/procedure for provision of pharmacy-directed monitoring in patients on medication regimens that lend themselves to therapeutic monitoring. Therapeutic drug monitoring is the utilization of pharmacokinetic and pharmacodynamic principles (often through drug concentrations) to optimize the safety and efficacy of a medication regimen.

Information:

All new orders for monitorable drugs will be assessed by a clinically trained pharmacist within 48 hours of initiation. If further monitoring is determined to be necessary by the pharmacist, the primary service will be contacted with the initial recommendation. At that time, the consulting pharmacist may request a verbal order for a pharmacy to dose order for that patient's medication regimen in order to continue to follow the medication regimen. Alternatively, at any time, a physician may choose to order a pharmacy to dose consult.

Pharmacy to Dose:

1. Any physician may request a pharmacist to provide therapeutic dosing and/or monitoring services for any specified pharmacologic agent. Such a request may be made by submitting a pharmacy to dose order in Sunrise Clinical Manager (SCM) or by giving a verbal order entered on his/her behalf.

    a. Such requests by the physician will result in the pharmacist being authorized to write orders for the initial drug dose, laboratory tests relevant to monitoring the drug, and/or subsequent orders for dosing adjustments as deemed appropriate by the pharmacist. Examples of these include ordering drug concentrations and/or assessments of renal/hepatic function relative to the dosing of an agent.

    b. At any time, the physician may alter the dosing and/or monitoring orders that have been initiated by the pharmacist.

    c. At any time, the physician may request the pharmacist discontinue the dosing/monitoring consult services being provided to a particular patient.

2. Upon receiving an order for pharmacy to dose a specific medication, a pharmacist will assess the patient and collect relevant information necessary to appropriately dose/monitor the specified drug so as to achieve therapeutic drug levels and minimize any potential risks of toxicity. Such items of information may include, but are not limited to:

    a. Indication for therapy (i.e. type and site of infection for antibiotic dosing/monitoring consults)
    b. Age

c. Sex
d. Height/Weight
e. Renal/Hepatic function
f. Estimated pharmacokinetic parameters
g. Medication history and/or time of last dose (if applicable)
h. Current/last known serum drug concentration (if applicable)

3. Upon selecting a dosing and/or monitoring plan, the pharmacist will enter applicable orders into SCM. Any orders written by the pharmacist in response to a pharmacy to dose order will be entered under the requesting physician with the specified source of “Per Protocol”.

4. The pharmacist will provide a progress note in the chart to provide information regarding the course of the dosing and/or monitoring services in accordance with department of pharmacy policies PH-02-04 and PH-02-05.

5. The pharmacist will be responsible for follow-up monitoring and/or dose adjustments if the pharmacist deems such actions necessary as documented in the progress notes.

Pharmacokinetic Guidelines
Refer to Clinical Pharmacokinetics Service and Anticoagulation Guidelines (updated annually)

UNIVERSITY OF KENTUCKY HOSPITAL
CHANDLER MEDICAL CENTER

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Clinical Laboratory Policy

Subject: Therapeutic Drug Monitoring (TDM) Laboratory Critical Value Call Policy

Purpose: To define guidelines for communicating supratherapeutic critical values at the University of Kentucky Medical Center.

Information:

- Supratherapeutic critical values for common TDM medications are listed in Appendix I.
- Supratherapeutic critical values (except cyclosporine, tacrolimus, and sirolimus) for patients admitted to a hospital service will be called to a pharmacist 24 hours a day based on the following schedule:
    - Monday through Friday from 8:00AM – 4:00PM: Critical values will be called to the pharmacist covering the medical service (list of service coverage will updated monthly by the Department of Pharmacy Services and provided to the TDM Lab Manager)
        - If no response in 30 minutes from initial page, then TDM lab will page the Pharmacy Resident on Call (Beeper #1875)
        - If no response in 30 minutes from initial page, then TDM lab will contact the pharmacist in the Central Pharmacy at 3-5641.
    - Monday through Friday from 4:00PM – 8:00AM: Critical values will be called to the Pharmacy Resident on Call (Beeper #1875)
        - If no response in 30 minutes from initial page, then TDM lab will contact the pharmacist in the Central Pharmacy at 3-5641.
    - On weekends (beginning Friday at 4:00PM and ending Monday at 8:00AM) and holidays, critical values will be called to the Pharmacy Resident on Call (beeper #1875)
        - If no response in 30 minutes from initial page, then TDM lab will contact the pharmacist in the Central Pharmacy at 3-5641.
- Immunosuppressants (cyclosporine, tacrolimus, and sirolimus) will be called to the transplant coordinator on the transplant service.
    - Heart/Lung: 330-2484
    - Renal: 323-5953, 323-6099, 323-5737
    - Liver: 323-4661
- Supratherapeutic critical values for patients in the Emergency Department not admitted to a hospital service and the University of Kentucky Clinics will called directly to the ordering physician.

Appendix I. THERAPEUTIC DRUG MONITORING (TDM) CRITICAL VALUE CALL CRITERIA
UKCMC 6th floor (HA 647) Phone# 323-6393
List of monitorable drugs and therapeutic ranges.

Monitorable Drugs	Lab Abbr.	Therapeutic Range *Metric Units*		Supratherapeutic values called to PHARMACIST	Lower Limit of Clinical Reportable Range	Upper Limit of Clinical Reportable Range	Therapeutic Range *International Units* (μmol/L)
acetaminophen	ACAM	10 – 30	μg/mL	>35.0	10.0	900	66 – 199
amikacin (peak)	AMIKP	25 – 35	μg/mL	>35.0	3.0	End Point	43 – 60
amikacin (trough)	AMIKT	5 – 10	μg/mL	>10.0	3.0	End Point	8.5 – 17
amikacin (random)	AMIKR	variable	μg/mL	>35.0	3.0	End Point	
carbamazepine	CRBZ	4 – 12	μg/mL	>15.0	0.2	60	17 – 51
carbamazepine (saliva)	FCRBZS	1.4 – 3.5	μg/mL	>6.0	0.5	20	6 – 15
cyclosporine	CSA	renal 100 – 200 cardiac 100 – 300 hepatic 100 – 300 lung 150 – 350	ng/mL	>400 called to transplant coordinator	25	2000	83 – 166 nmol/L 83 – 249 nmol/L 125 – 290 nmol/L
digoxin	DIG	0.8 – 2.0	ng/mL	>2.3	0.5	13.5	1.0 – 2.6 nmol/L
gentamicin (peak)	GENTP	5 – 10	μg/mL	>10.0	0.5	36.0	10.5 – 21
gentamicin (trough)	GENTT	< 2.0	μg/mL	>2.0	0.5	36.0	<4.2
gentamicin (random)	GENTR	variable	μg/mL	>10.0	0.5	36.0	variable
lidocaine*	LIDO	1.5 – 6.5	μg/mL	>6.5	1.0	10.0	6.4 – 27.8
lithium	LIT	0.6 – 1.2	mmol/L	>1.2	0.1	End point	0.6 – 1.2
methotrexate	MTRX	≥5 @ 24hrs ≥0.5 @ 48hrs ≥0.05 @ 72hrs ≥0.02 @ 1-2 weeks	μmol/L	called to floor	0.01	2000	≥5 @ 24hrs ≥0.5 @ 48hrs ≥0.05 @ 72hrs ≥0.02 @ 1-2 weeks
phenobarbital	PHNO	15 – 40	μg/mL	>45.0	5.0	240	65 – 172
phenobarbital (saliva)	FPHNOS	5 – 15	μg/mL	>18	5	240	21.6 – 64.7
phenytoin (total)	PHTN	10 – 20	μg/mL	>22.0	2.5	40.0	40 – 79
phenytoin (free)	FPHTN	0.8 – 1.6	μg/mL	>1.6	0.5	12.0	3.2 – 6.4
phenytoin (saliva)	FPHTN	1 – 2	μg/mL	>2.2	0.5	4.0	4 – 8
primidone*	PMDN	5 – 12	μg/mL	>15.0	0.1	End point	23 – 55
procainamide*	PROC	4 – 10	μg/mL	sum >30	0.2	End point	17 – 42
(N-acetyl) procainamide*	NAPA	NA	μg/mL	sum >30	0.3	End point	-
quinidine*	QUIN	2 – 5	μg/mL	>5	0.2	End point	6.2 – 15.4
salicylate	ASAS	< 25	μg/mL	>30.0	5.0	300	-

List of monitorable drugs and therapeutic ranges. (cont.)

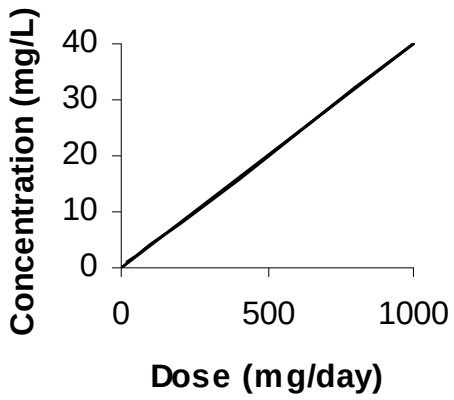
Monitorable Drugs	Lab Abbr.	Therapeutic Range *Metric Units*		Supratherapeutic values called to PHARMACIST	Lower Limit of Clinical Reportable Range	Upper Limit of Clinical Reportable Range	Therapeutic Range *International Units* (μmol/L)
sirolimus	SIRO	3-20	ng/mL	>15 called to transplant coordinator	2.0	50.0	-
tacrolimus	TACRO	4-17	ng/mL	>25 called to transplant coordinator	2.0	50.0	5-21
theophylline	THEO	10 – 20 (bronchodilator) 6 – 13 (neonatal apnea)	μg/mL	>22.0 >13.0	2.0	120.0	55.5 – 111 33 – 72
tobramycin (peak)	TOBP	5 – 10	μg/mL	>10.0	0.5	36.0	10 – 21
tobramycin (trough)	TOBT	< 2.0	μg/mL	>2.0	0.5	36.0	<4
tobramycin (random)	TOBR	variable	μg/mL	>10.0	0.5	36.0	variable
valproic acid	VALP	50 – 100	μg/mL	>120.0	10.0	450.0	346 – 693
vancomycin (peak)	VANCP	20 – 40	μg/mL	>40.0	5.0	150.0	14 – 28
vancomycin (trough)	VANCT	5 – 15 15 – 20 (life threatening infections)	μg/mL	>20.0	5.0	150.00	3 – 10 10 – 14
vancomycin (random)	VANCR	variable	μg/mL	>40.0	5.0	150.00	variable

Sent to outside laboratory and may require 2-3 days to report results. End point = sample can be diluted up to 3X.

Basic Pharmacokinetic Concepts:

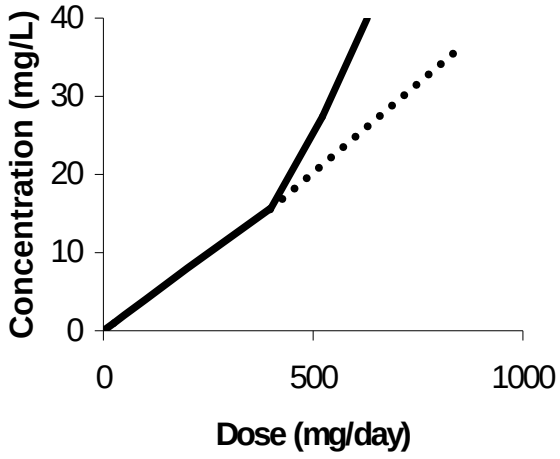
Linear pharmacokinetics:

- Serum concentrations change proportionally with increase in dose (e.g., increase dose from 500mg/day to 1000mg/day, concentrations and AUC double).
- Most drugs follow linear pharmacokinetics



Nonlinear or Michaelis-Menten pharmacokinetics:

- As dose increases, a disproportionately greater increase in plasma concentration is achieved
- **Vmax = maximum amount of drug that can be metabolized per unit time (mg/day)**
- **Km = Michaelis-Menten constant, representing the concentration of phenytoin at which the rate of this enzyme-saturable hepatic metabolism is one-half of maximum**
- Classic example: phenytoin



$$\text{Drug elimination rate} = \frac{dX}{dt} = \frac{Vmax*Css}{Km+Css}$$

$$C_{ss} = \frac{\left(\frac{\text{Dose}}{\tau}\right)(S)(F)(K_m)}{(V_{max}) - \left[\left(\frac{\text{Dose}}{\tau}\right)(S)(F)\right]}$$

Clearance (Cl_s):

- Represents the volume of plasma (or blood) from which drug is removed, in a given time period
- Expressed in volume/time (e.g., ml/min, L/hr)
- Most IMPORTANT pharmacokinetic parameter $Cl_s = Cl_{Hep} + Cl_{Ren} + Cl_{Other}$
- Model-independent parameter used to estimate average steady-state concentrations and adjust maintenance doses ("c-bar equation"):

$$\overline{C} = \frac{Ko}{Cl_s}; \quad \overline{C} = \frac{S \cdot F \cdot X_o}{Cl_s \cdot \tau} \quad \text{or} \quad Cl_s = \frac{S \cdot F \cdot X_o}{\overline{C} \cdot \tau} \quad \text{or} \quad X_o = \frac{Cl_s \cdot \overline{C} \cdot \tau}{S \cdot F}$$

- **Relationship between K, Vd, and Cl:**

$$K = \frac{Cl_s}{Vd} \quad \text{or} \quad Cl_s = Vd*K; \quad \text{NOTE: Vd and } Cl_s \text{ are INDEPENDENT VARIABLES}$$

- **Hepatic Clearance (Cl_{Hep})**

$$\text{Extraction (E)} = \frac{f_{ub}*Cl_{Int}}{Q_H + (f_{ub}*Cl_{Int})}$$

where Q_H = hepatic blood flow; f_{ub} = fraction unbound; Cl_{int} - intrinsic clearance

$$Cl_{Hep} = Q_H \text{ X } E$$

$$Cl_{Hep} = \frac{Q_H*f_{ub}*Cl_{Int}}{Q_H + (f_{ub}*Cl_{Int})}$$

For HIGH EXTRACTION (>70%) drug, $f_{ub}*Cl_{Int}$ >>>>> Q_H, the equation reduces to:

$$Cl_{Hep} = Q_H$$

For LOW EXTRACTION (<30%) drug, Q_H >>>>> $f_{ub}*Cl_{Int}$, the equation reduces to:

$$Cl_{Hep} = f_{ub}*Cl_{Int}$$

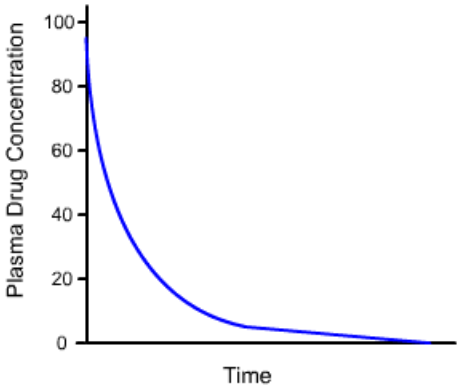
- **Renal Clearance (Cl_{Ren})**

$$Cl_{Ren} = Cl_{GFR} + Cl_{TS} - Cl_{TR}$$

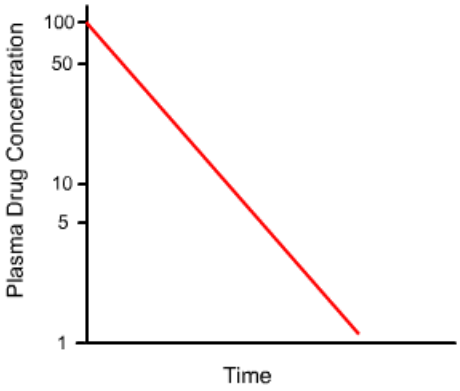
GFR = glomerular filitration rate, TS = tubular secretion, TR = tubular reabsorption

Half-life (t½) & elimination rate (K):

- Elimination t½ = time required for serum concentration to decrease by ½ <u>after</u> absorption & distribution phase
- Expressed in hours or minutes
- Takes approximated 3-5 half-lives to reach steady-state
- Dependent variable (depends on Cls and Vd): $t_{½} = \frac{0.693 \cdot Vd}{Cl}$ or $t_{½} = \frac{0.693}{K}$
- Clinically, can be calculated by 2 concentrations: $t_{½} = \frac{\ln C_1/C_2}{K}$
- Most drugs follow first-order elimination



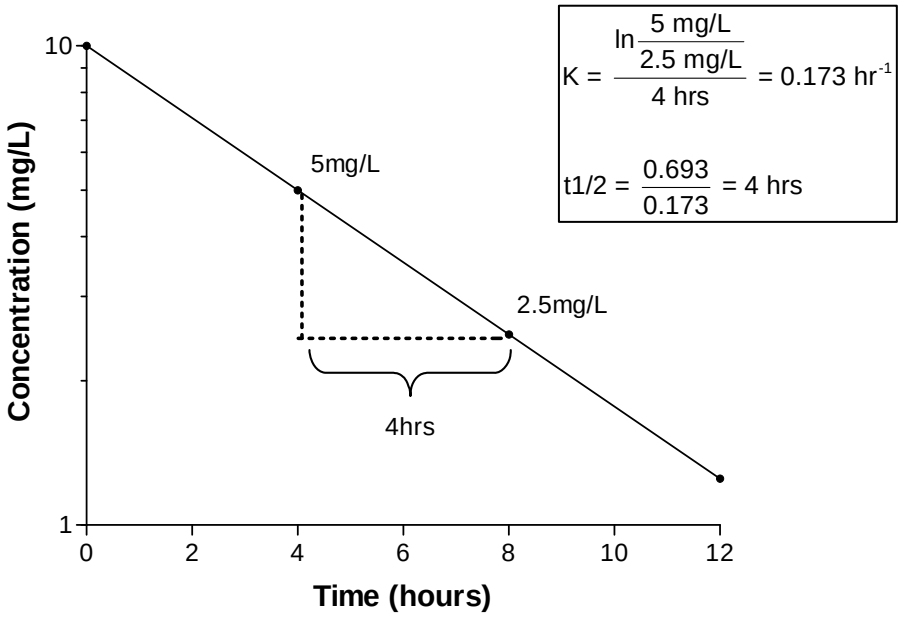
Plasma drug concentration versus time after an intravenous (bolus) drug dose, assuming a one-compartment model with first-order elimination (linear y-scale).



Same with a log scale y-axis.

- K = fraction of the drug in the body eliminated over time:

$$K = \frac{\ln C_1/C_2}{T'} \text{ or } K = \frac{0.693}{t_{½}}$$



$$K = \frac{\ln \frac{5 \text{ mg/L}}{2.5 \text{ mg/L}}}{4 \text{ hrs}} = 0.173 \text{ hr}^{-1}$$

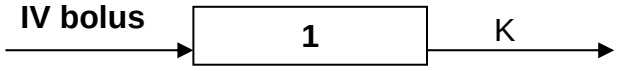
$$t1/2 = \frac{0.693}{0.173} = 4 \text{ hrs}$$

Volume of distribution (Vd):

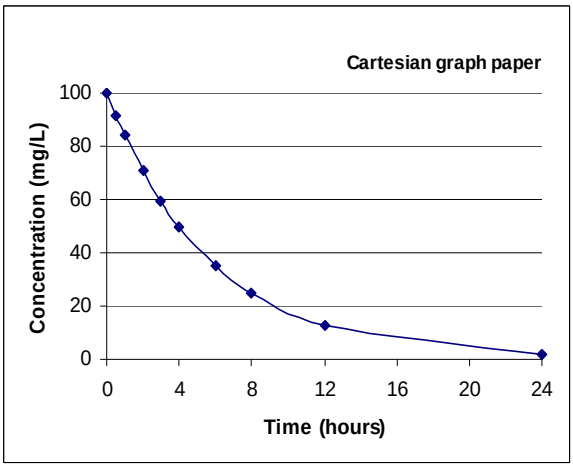
- Vd is a hypothetical volume that is the proportionality constant that relates amount of drug in body to the serum concentration.
- Expressed in liters (L) or liter/kg (L/kg).
- Drugs distribute based on composition of body fluids and tissues.
- $Vd = \frac{X_o}{C_o}$ where X_o = dose administered; C_o = initial concentration
- Useful for calculating loading dose: $LD = Vd \cdot C$
- Can calculate Vd using steady-state peak concentration after multiple dosing:

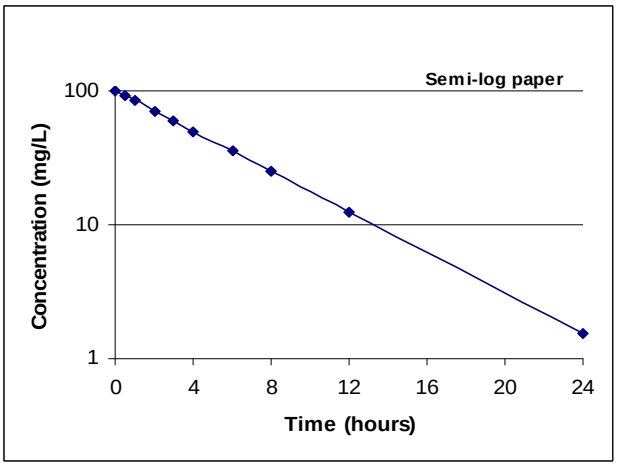
$$Vd = \frac{K_o(1-e^{-Kt})\, e^{-KT}}{C_{pk}^{ss} \cdot K(1-e^{-K\tau})}$$

One-compartment model



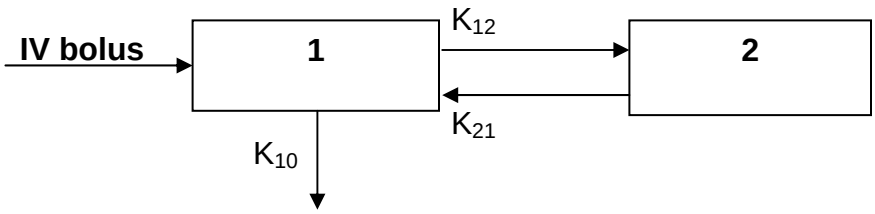
- 1-compartment model with first-order elimination following IV bolus:

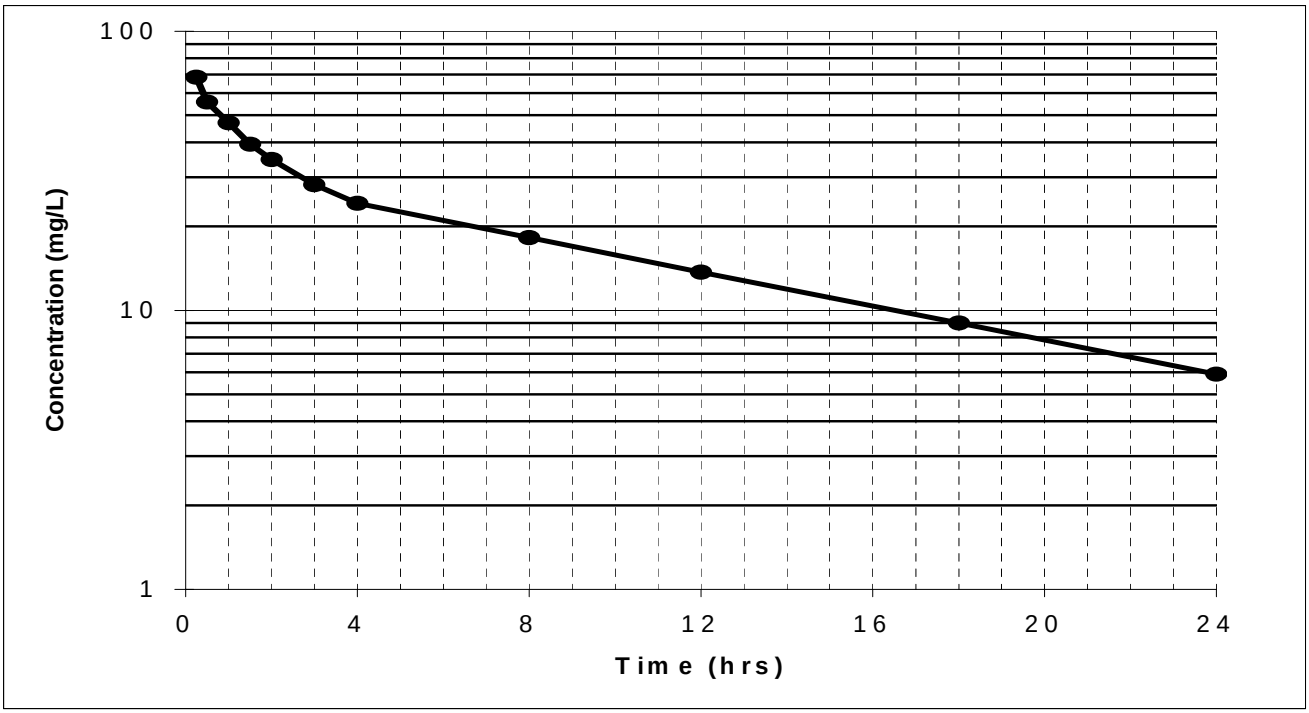




Two-compartment model:

- Many drugs follow 2-compartment model (see model and concentration-time plot below)
- However, 1-cpt model is sufficient to individualize doses of selected drugs (e.g., aminoglycosides, vancomycin) in the clinical setting **if** concentrations are drawn appropriately.





Multiple dosing and steady-state equations:

$$C_{pk}^{ss} = \frac{K_o(1-e^{-Kt})\,e^{-KT}}{Vd \cdot K(1-e^{-K\tau})}$$

C_{pk}^{ss} = concentration (referred to as peak) drawn at T, time post infusion

Ko = dosing rate in mg/hr

K = elimination rate in hr^{-1}

t = infusion time in hours (e.g., usually 0.5hrs for aminoglycosides)

T = post infusion time in hours that corresponds with C_{pk}^{ss} (e.g., usually 0.5hrs for aminoglycosides)

Vd = Volume of distribution in liters

τ = Tau, dosing interval in hours

This equation is used for aminoglycosides and vancomycin which when dosed as intermittent IV infusion.

You can build the steady-state multiple dosing equation using the following equations (also see next page):

1. The infusion (e.g., 30 min for aminoglycosides, 60 min for vancomycin) is a continuous infusion:

   $$C = \frac{Ko\ (1\text{-}e^{-kt})}{Cl} \quad \text{or} \quad \frac{Ko\ (1\text{-}e^{-kt})}{Vd \cdot K}$$ where t = infusion time

   This above equation will calculate the concentration at the end of an intermittent IV infusion following the first dose (assuming 1-cpt model and 1st order elimination).

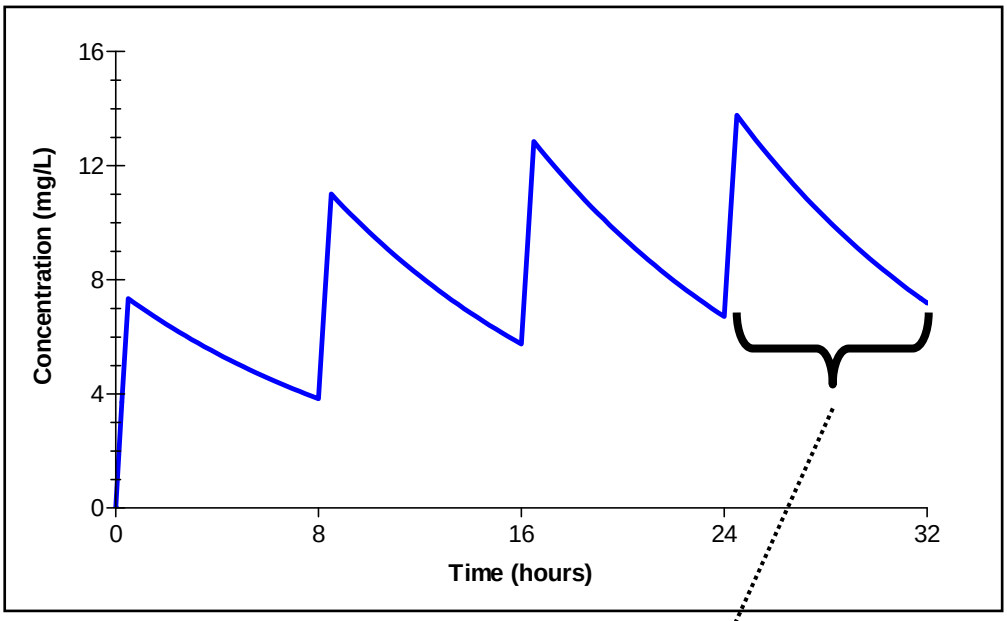
2. Peak concentrations are obtained post-distributional to fit a 1-cpt model so the concentration must be eliminated the time after the end of the infusion (e.g., aminoglycosides = 30min; vancomycin = 60min). This can be accounted for by eliminating the concentration by multiplying the concentration by e^{-kT} where T = time post infusion resulting in the following equation:

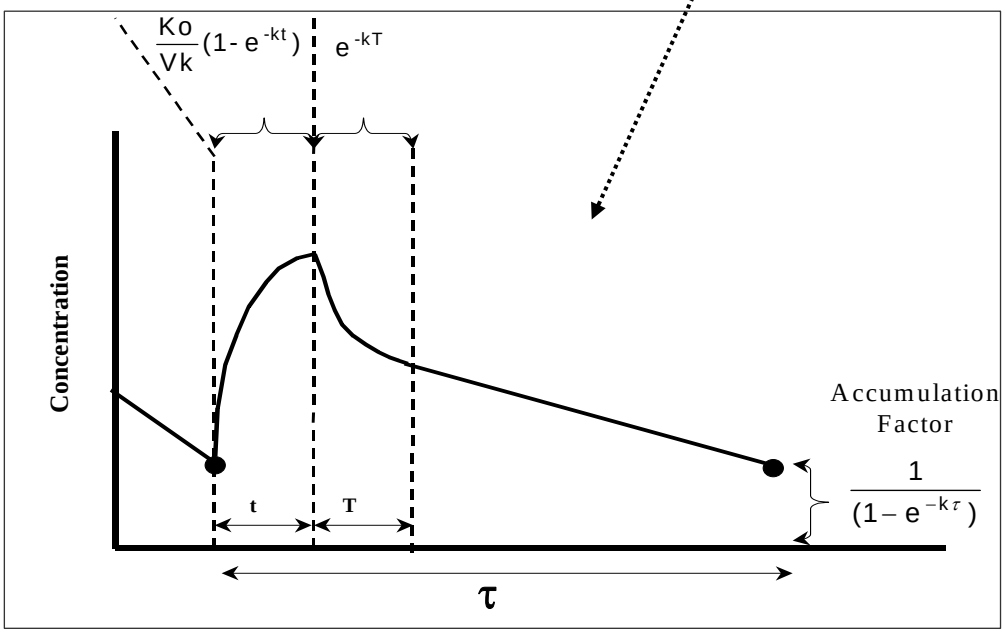
   $$C_{1st\ dose}^{pk} = \frac{Ko\ (1\text{-}e^{-kt})}{Vd \cdot K} \cdot e^{-kT}$$

3. Concentrations are obtained at steady-state so accumulation must be considered using the following equation: $\frac{1}{1\text{-}e^{-k\tau}}$ resulting in the final equation:

   $$C = \frac{K_o\ (1\text{-}e^{-kt})}{Vd \cdot K} \cdot e^{-kT} \cdot \frac{1}{1\text{-}e^{-k\tau}} = \quad C_{pk}^{ss} = \frac{K_o(1-e^{-Kt})\,e^{-KT}}{Vd \cdot K\ (1-e^{-K\tau})}$$

Multiple dosing of intermittent infusion (0.5 hr infusion every 8 hrs)





Pharmacokinetic/dynamic Relationships of Antibiotics

Pharmacokinetic/dynamic (PK/PD) Terminology

- **General concepts:**
  - All PK/PD indices should include unbound fraction of drug or degree of protein binding
  - Should be stated whether doses were steady-state or single dose
  - Linearity between dose and PK parameter must be included
  - Source: Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs. (*Int J Antimicrob Agents*. 2002;19(4):355-8.)
- **MIC - minimum inhibitory concentration (e.g., mg/L)**, the least amount of drug that prevents visible growth of a predetermined number of organisms (usually 90%)
- **MBC – minimum bactericidal concentration (e.g., mg/L)**
- **AUC or $AUC_{0\text{-}24hr}$ (e.g., mg/L*hr)–** The area-under-the-concentration time curve over 24 hrs, preferably at steady-state. AUC is a good index of antibiotic exposure, and it depends directly on dose, but is influenced by absorption (F) and clearance (Cl):

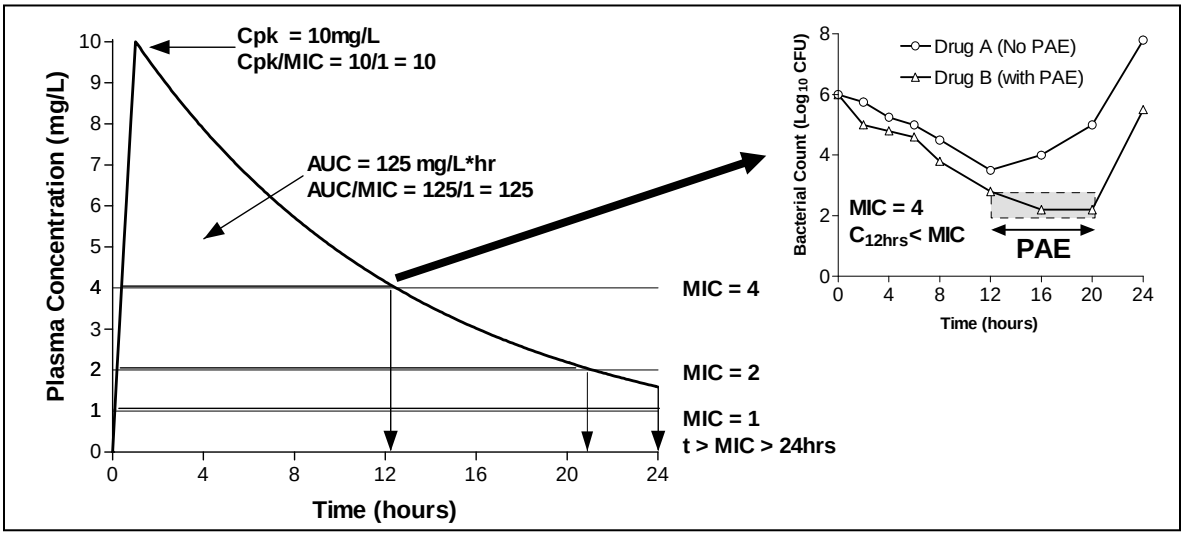
$$AUC = \frac{F * Dose}{Cl}$$

- **AUC/MIC or AUC_{24hrs}/MIC (hrs)** – AUC divided by MIC**,** usually over 24 hours
- **AUIC (hrs) – area under the inhibitor curve using actual inhibitory titers.** *Note, different definitions have been used including AUC/MIC so be careful interpreting literature.*
- **C_{pk} or C_{max} (mg/L) – Maximum serum antibiotic concentration.** Must consider whether under steady-state conditions and if concentration drawn during distribution phase
- **C_{pk}/MIC ratio – peak concentration divided by the MIC**
- **Time (t) > MIC (%)–** cumulative percentage of time over 24hr period that the drug concentration exceeds the MIC at steady-state conditions during the dosing interval
- **Post antibiotic effect (PAE, hrs)** –the persistent suppression of bacterial growth following exposure and removal of an antibiotic. Reflects bacterial "recovery time". Can be *in vitro* or *in vivo*
  - **Possible mechanisms:** Non-lethal damage by the antibiotic, persistence of drug on drug-receptor binding site after concentrations are <MIC, & phagocytosis by leucocytes.
  - **Factors that influence:** Type of organism, inoculum, drug concentration (higher the better), duration of therapy, type of antibiotic, & presence of immune cells

How are Clinical and Microbiologic Outcomes determined?

- Clinical success usually described as failure, improvement, or cure
  - Rate of symptom resolution/free period (e.g., duration of fever, WBCs, chest X-ray)
  - Hospital length of stay and readmission rate
  - Mortality rate
- Microbiologic outcomes: bacterial eradication at site of infection (negative cultures)

Plot demonstrating PK/PD relationships using MIC:



Bactericidal versus Bacteriostatic

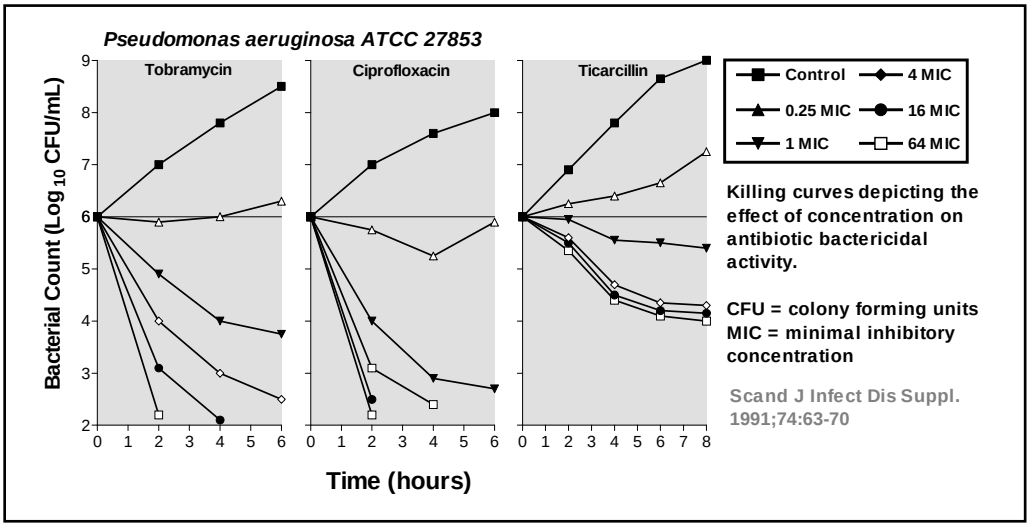
- **'static = inhibits growth of organisms**
  - MBC >>>MIC
  - Usually inhibitors of protein synthesis (e.g., macrolides, clindamycin, linezolid)
- **'cidal = kills the organism**
  - MBC ≈ MIC
  - Usually inhibitors of cell wall or DNA synthesis (e.g., aminoglycosides, fluoroquinolones)
- Does NOT describe the relationship between antibiotic concentration & time course of killing

Concentration-dependent killing

- Higher the concentration, the greater the rate & extent of bactericidal activity
- **C_{pk}/MIC ratio or AUC/MIC correlate with activity**
- e.g., aminoglycosides, fluoroquinolones, metronidazole

Minimal-concentration or time-dependent killing

- Saturation of the killing rate occurs at LOW multiples of the MIC - usually 4-5X
- Largely dependent on the **TIME OF EXPOSURE, t>MIC**
- e.g., β-lactams, vancomycin, clindamycin, macrolides



β-lactams

- Exhibit time-dependent killing & usually bactericidal
- Clinical response with AUC/MIC but **t>MIC of dosing interval (DI) is a better predictor**
- **Gram+ organisms (*in vitro* & animal studies): t>MIC for ≥40–50% of DI** *(Clinical Infectious Diseases* 2001;33:S233-S237)

- **Pediatric patients with otitis media (with *S. pneumoniae*):** Positive correlation between **t>MIC for ≥40-50% of DI** & **bacteriological cure rates** (*Pediatric Infect Dis J* 1996;15:255-9 & *Arch Intern Med* 2000; 160:1399-1408)
- **Gram- organisms (animals): t>MIC ≥60–70% of DI may be required**
- **Patients with Gram- nosocomial pneumonia:** Positive correlation between **AUC_{0-24hr} (>140)** and t>MIC of cefmenoxime, 3rd-gen cephalosporin (*Am J Med* 1984;77:43-50)

- Several preliminary studies have investigated **continuous infusion of β-lactams** as a more rational dosing method to achieve a **greater t>MIC**
  - **Other potential advantages:** Lower costs, less "peak" adverse effects, convenience with once-daily set up & delivery of drug (e.g., home infusion therapy)
  - **Potential problems:** Drug stability/compatibility, delayed tissue equilibration (must provide initial loading dose), & susceptibility to inoculum effect
  - **Unresolved issues:** Lack of well-defined goal steady-state concentration/MIC ratio, & possible need for TDM of serum concentrations with lower daily doses
  - Piperacillin/tazobactam continuous infusion dosing nomogram used at Hartford Hospital:

	Standard Regimen	Nosocomial Regimen*
Loading dose	2.25 gm over 30 mins	2.25 gm over 30 mins
Continuous infusion	*Clcr ≥ 20ml/min:* 8 gm/1 gm in 150 ml NS @ 7 ml/hr	*Clcr > 40ml/min:* 12 gm/1.5 gm in 150 ml NS @ 7 ml/hr *Clcr = 20 - 40ml/min:* 8 gm/1 gm in 150 ml NS @ 7 ml/hr

*Nosocomial infection: infection developing 48 hrs after admission or suspected *Pseudomonas aeruginosa;* Exclusions: Patients with Clcr < 20 ml/min or limited IV line access. Source: *Pharmacotherapy*. 2002 Apr;22(4):471-83.

Fluoroquinolones

- Typically considered to be bactericidal with concentration-depending killing
- **Cpk/MIC** & **AUC_{0-24hr}/MIC** thought to be best predictive parameters
- However, there is much debate over what are PK/PD breakpoints:

(1) Schentag et al. (*Ann Pharmacotherapy* 2003;37(9):1287-98.)

- Uses AUIC as AUC_{0-24hr}/MIC.
- Based on *in vitro* & animal data using bacterial strains with marginal susceptibility to fluoroquinolones (*P. aeruginosa*, *S. aureus*, & *S. pneumoniae*)
- AUC_{0-24hr}/MIC <30-50 or Cpk/MIC ratio of 5:1, activity is bacteriostatic

- $AUC_{0\text{-}24hr}$/MIC >100 - <250, activity is bactericidal but at a slower rate (therapy needed for 7 days)
- $AUC_{0\text{-}24hr}$/MIC >250 or Cpk/MIC ratio of 25:1, demonstrate rapid concentration-dependent killing and bacterial eradication within 24hrs
- Proposes $AUC_{0\text{-}24hr}$/MIC >250 may be necessary for rapid bactericidal action regardless whether bacteria is gram- or gram+

(2) Rapp & Campion and Zhanel & Norreddin

- Different ratios are required for different organisms
- For gram+ bacteria (e.g., *S. pneumoniae*), $AUC_{0\text{-}24hr}$/MIC of 30-50 is sufficient based on clinical and *in vitro* data currently available
- For gram- bacteria, $AUC_{0\text{-}24hr}$/MIC of 100-125 is sufficient until more data is available
- Previous studies have limitations, need to include unbound drug in PK/PD analysis
- Better quantification of bacterial killing/regrowth curve needed
- Presence of resistant strains should be evaluated including analyzing genetic composition

Aminoglycosides

- Exhibit **concentration-dependent killing** for gram- bacteria (possibly time-dependent for gram+ organisms)
- **C_{pk}/MIC ratio is most commonly linked to clinical outcomes** but AUC/MIC has been shown equal or better in animal studies
- To obtain >90% clinical response, suggested that Cpk exceed the MIC by ~10X. **This is theoretical rationale for administering higher dose (5-7mg/kg) with extended interval (q24hrs).**
  - Once daily dosing of aminoglycosides originally based on *Pseudomonas aeruginosa* MIC ~2, goal Cpk ~ 20mg/L and Cpk/MIC ratio = 10:1 based on 7mg/kg dosing for gentamicin and tobramycin. (*Antimicrob Agents Chemother.* 1995 Mar;39(3):650-5.)
  - Note, there is much debate regarding appropriate time to monitor Cpk since larger doses (7mg/kg) have extended volume of distribution

- Exhibit **concentration-dependent PAE** for gram- bacteria ranging 2-10 hours (animal models)
- Subject to **adaptive resistance**, *short-term decrease or down-regulation in drug uptake & subsequent reduction in bactericidal activity after prolonged exposure to low drug concentrations*
- ODA dosing may reduce **adaptive resistance** by saturating drug uptake
- $AUC_{0\text{-}24hr}$ of 70-100 mg/L*hr has been proposed as “therapeutic” range to prevent toxicity

Vancomycin

- Exhibit time-dependent killing & usually bactericidal by inhibition of bacterial cell wall synthesis
- t>MIC and possibly AUC/MIC correlate better with bactericidal activity. However, there are limited data suggesting a relationship between serum drug concentration and clinical outcomes or toxicity

  - A few studies have found better bacteria eradication with trough concentrations > 10mg/L (*Pharmacotherapy* 1995;15:85-91 and).
- PAE of 2-3 hrs against gram+ bacteria
- Vancomycin requires actively growing bacteria to exert its effect

Macrolides

- Although generally bacteriostatic, clarithromycin and azithromycin are bactericidal against *S. pyogenes*, *S. pneumoniae*, and *H. influenzae*
- Intracellular vs. extracellular concentrations and tissue penetration make it difficult to predict activity
- PAE variable
- Erythromycin and clarithromycin: t> MIC is best PK/PD parameter
- Azithromycin: Best correlated with $AUC_{0\text{-}24hrs}$/MIC

Other Antibiotics (Refer to the table on next 2 pages)

Pharmacokinetic and pharmacodynamic characteristics of selected antimicrobials.

Antimicrobial Agent	Pharmacokinetic properties *(In adult patients with normal renal & hepatic function)*				Pharmacodynamic properties *(Activity against pathogens for which the agent is typically used.)*			
	F (%)	Vd (L/kg)	$t_{½\ \beta}$ (h)	Dosage Interval (h)	Activity	Killing	Gram negative PAE	PK-PD parameter best correlating with clinical efficacy
β-Lactams								
Benzylpenicillin and phenoxymethylpenicillin (oral)	15 (60)	0.29	0.5	4–6	Bactericidal	T	N	t>MIC
Cloxacillin	50	0.08–0.11	0.5	4–6	Bactericidal	T	N	t>MIC
Ampicillin and amoxicillin	40 (75)	0.18–0.35	1.0	4–6	Bactericidal	T	N	t>MIC
Piperacillin		0.15–0.21	1.3	4–6	Bactericidal	T	N	t>MIC
Ticarcillin		0.17–0.25	1.2	4–6	Bactericidal	T	N	t>MIC
Cefazolin		0.10–0.18	1.8	8	Bactericidal	T	N	t>MIC
Cefuroxime	52	0.16–0.24	1.3	8	Bactericidal	T	N	t>MIC
Ceftriaxone		0.13–0.19	8.0	12–24	Bactericidal	T	N	t>MIC
Ceftazidime		0.21–0.25	1.8	8	Bactericidal	T	N	t>MIC
Imipenem		0.18–0.28	1.0	6	Bactericidal	T	Y	t>MIC
Meropenem		0.37–0.49	1.0	8	Bactericidal	T	Y	t>MIC
Aztreonam		0.14–0.18	2.0	8	Bactericidal	T	N	t>MIC
Glycopeptides								
Vancomycin		0.7–0.9	6–8	12	Bactericidal	T	N	t>MIC, AUC/MIC
Fluoroquinolones								
Ciprofloxacin	70–85	1.7–3.7	2.5–5.3	12	Bactericidal	C	Y	C_{max}/MIC, AUC/MIC
Levofloxacin	85–95	1.2–1.5	6.5–7.4	12–24	Bactericidal	C	Y	C_{max}/MIC, AUC/MIC
Gatifloxacin	95	1.5–2.2	6.5–8.4	24	Bactericidal	C	Y	C_{max}/MIC, AUC/MIC
Moxifloxacin	85	2.1–3.5	9.1–15.6	24	Bactericidal	C	Y	C_{max}/MIC, AUC/MIC
Aminoglycosides								
Gentamicin		0.21–0.41	2.5	8–24	Bactericidal	C	Y	C_{max}/MIC, AUC/MIC
Tobramycin		0.25–0.41	2.5	8–24	Bactericidal	C	Y	C_{max}/MIC, AUC/MIC
Amikacin		0.21–0.33	2.5	8–24	Bactericidal	C	Y	C_{max}/MIC, AUC/MIC

Pharmacokinetic and pharmacodynamic characteristics of selected antimicrobials (cont).

Antimicrobial Agent	Pharmacokinetic properties *(In adult patients with normal renal & hepatic function)*				Pharmacodynamic properties *(Against pathogens for which the agent is typically used)*			
	F (%)	Vd (L/kg)	$t_{½\ \beta}$ (h)	Dosage Interval (h)	Activity	Killing	Gram negative PAE	PK-PD parameter best correlating with clinical efficacy
Macrolides								
Erythromycin	18–45	0.34–1.2	2–4	6	Bacteriostatic	T	N	t>MIC
Clarithromycin	50	2.1–3.1	5–7	12	Bacteriostatic	T	N	t>MIC
Azithromycin	37	31		24	Bacteriostatic	T	N	AUC/MIC
Lincosamides								
Clindamycin	90	0.8–1.4	2.4	8	Bacteriostatic	T	N	t>MIC
Streptogramins								
Quinupristin/dalfopristin		0.45/0.24	1.5	8	Bactericidal	C	N	AUC/MIC, AUC/MBC
Oxazolidinones								
Linezolid	100	0.57–0.71	5	12	Bacteriostatic	T	N	t>MIC
Other								
Metronidazole	95	0.64–0.84	6–14	12	Bactericidal	C	N	C_{max}/MIC, AUC/MIC

F = Bioavailability; Vd = Volume of distribution; $t_{½\beta}$ = elimination half-life; T = Time-dependent killing; C = concentration-dependent killing; Y = yes; N = no. Adapted from: *Clin Pharmacokinet.* 2003;42(9):793-817.

GENERAL GUIDELINES FOR PHARMACOKINETIC MONITORING

I. When a patient is on a monitorable drug

A. Assess the necessity for serum drug concentrations and address this issue with the medical team.

B. Avoid problems with interpretation of upcoming concentrations by:

1. Obtaining the concentration at steady-state if possible.
2. Avoiding ordering concentrations during third shift.
3. Ascertaining that the nurse has marked the appropriate dose for obtaining concentrations on the MAR (*ex. Doses may have been given in the ER or documented in different areas of the medical records*).
4. Staggering penicillin doses away from the dose of an aminoglycoside around which concentrations are drawn (*ideal if penicillin dose is given at least 2 hours apart from aminoglycoside dose*).

II. When a concentration is obtained

A. Using the collect/received time reported in the lab computer and the MAR, verify that the concentration is a peak or a trough.

B. Document that the doses preceding the concentration were on time to verify that the concentration represent steady-state conditions.

C. Calculate the appropriate pharmacokinetic parameters and compare with predicted population values.

D. Write concise notes including kinetic parameters on all concentrations, whether therapeutic or subtherapeutic. (*See sample notes on pages 32 & 107*).

E. Document any information, not retrievable from the medical records, that was used in making your calculations or recommendations (*weight, height, or information obtained directly from the patient or healthcare provider).*

Remember… appropriate documentation will:

1. Improve the quality of care;
2. Allow continuity of care when changing services;
3. Document your role in patient management;
4. Protect you legally;
5. Protect you professionally in audits on quality of care.

III. How does Clinical Pharmacokinetic Monitoring fit into the Pharmaceutical Care Process?

Pharmacist's primary responsibilities in PCare:

- Identifying a patient's actual and potential drug-related problems
- Resolving the patient's actual drug-related problems
- Preventing the patient's potential drug-related problems from becoming actual problems

Clinical Pharmacokinetics role in PCare:
Identifying and resolving potential problems if the patient is:

- Taking or receiving the wrong dose of the correct drug
- Experiencing an adverse drug reaction
- Experiencing a drug-drug or drug-food interaction

Pharmacist's Role in Clinical Pharmacokinetic Monitoring
(Am J Health Syst Pharm. 1998 Aug 15;55(16):1726-7*)*

- Designing patient-specific drug dosage regimens based on pharmacologic characteristics of the drugs used, the objectives of drug therapy, concurrent diseases & drug therapy, and other pertinent patient factors.
- Monitoring & adjusting dosage regimens based on pharmacologic responses and on biological fluid (e.g. plasma, serum, blood, CSF) and tissue drug concentrations in conjunction with clinical signs and symptoms or other biochemical parameters.
- Evaluating unusual patient responses to drug therapy for possible pharmacokinetic and pharmacologic explanations.
- Communicating, verbally and in writing, information on patient-specific drug therapy to physicians, nurses, and other clinical practitioners.
- Educating pharmacists, physicians, nurses, and other clinical practitioners on pharmacokinetic principles and/or appropriate indications for clinical pharmacokinetic monitoring.
- Recommending assays or procedures for the analysis of drug concentration in order to facilitate the evaluation of dosage regimens.
- Developing quality assurance programs to document improved patient outcomes and economic benefits resulting from clinical pharmacokinetic monitoring.

GENERAL EQUATIONS for BSA, IBW, and Clcr

Equations for body surface area (BSA):

$$BSA\ (m^2) = \frac{[\ Wt(kg)^{0.425}\ x\ Ht(cm)^{0.725}\ x\ 71.84\ ]}{10{,}000}$$ (Dubois; Arch Internal Med 1916;17:863)

$$BSA\ (m^2) = \frac{\sqrt{Ht(cm)\ x\ Wt(kg)}}{60}$$ (Mosteller; NEJM 1987;317:1098)

Equation for Ideal Body Weight (IBW):

IBW (male, kg) = 50 + (2.3 x ea. inch over 5 ft)

IBW (female, kg) = 45 + (2.3 x ea. inch over 5 ft)

(Devine; Drug Intell Clin Pharm 1974;8:650)

Estimation of GFR using serum creatinine (Scr)

- Creatinine is endogenous substance derived from muscle metabolism, small & not bound to plasma proteins, maintains a fairly constant level, and predominantly filtered ~85% (~15% TS) with minimal non-renal elimination.
- Proportional to muscle mass & body weight
- Normal 24-hour excretion: 20-25 mg/kg IBW (males) and 15-20mg/kg (females)
- Creatinine production decreases with age: 2mg/kg/24hrs per decade
- Several equations have been published to predict GFR using creatinine clearance (Clcr)

Estimation of GFR using Cockcroft-Gault Equation:

(Male) $Clcr_{(ml/min)} = \frac{(140\text{-age})(ABW)}{(72)(Scr)}$; (Female) Multiply by 0.85

ABW = actual body weight

Note: Use ABW unless obese (>125% ideal body weight), suggest use Salazar & Corcoran equation.

$$Clcr\ (\text{standardized to BSA, ml/min/1.73m}^2) = Clcr\ X\ \frac{1.73m^2}{BSA}$$

- Most commonly used equation for estimating GFR in clinical practice
- Derived from multiregression analysis
- Relationship includes corrections of creatinine production for age, weight, and gender
- Several limitations (best for patients with average muscle mass and stable production of creatinine)
- *Should be used with caution in patients with changing Scr (e.g., acute renal failure), low Scr (e.g., lack of mobility, patients with loss of muscle mass, spinal cord injury), and severe renal insufficiency.*

Estimation of GFR in obese patients (>125% X IBW) using Salazar-Corcoran Equation:

$$\text{(Male) } Clcr_{(ml/min)} = \frac{[137\text{-Age}] \times [(0.285 \times Wt) + (12.1 \times Ht^2)]}{(51 \times Scr)}$$

$$\text{(Female) } Clcr_{(ml/min)} = \frac{[146\text{-Age}] \times [(0.287 \times Wt) + (9.74 \times Ht^2)]}{(60 \times Scr)}$$

Wt = actual body weight in kg; Ht = height in meters

Note: Ht should be converted to meters before squared (i.e. 6'0" = 72" = 183cm = 1.83m)

Estimation of GFR by calculating Clcr from 24-hour urine collection:

$$Cl_{cr\ (ml/min)} = \frac{\text{creatinine production rate (mg/1440min)}}{\text{Scr (mg/100ml)}}$$

$$= \frac{Ucr \times \left(\frac{1dL}{100ml}\right) \times Uvol \times \left(\frac{1}{1440min}\right)}{Scr \times \left(\frac{1dL}{100ml}\right)}$$

Ucr = urine creatinine concentration (mg/dL);

Uvol = total urine volume (ml/24 hrs);

Scr = serum creatinine (mg/dL)

Modification of Diet in Renal Disease (MDRD) Equation (Ann Intern Med. 1999 Mar 16;130(6):461-70.)

MDRD study equation:

$GFR\ (ml/min/1.73m^2) = 170 \times [Scr]^{-0.999} \times [Age]^{-0.176} \times [BUN]^{-0.170} \times [Alb]^{0.318}$

$\times$ [0.762, if female] $\times$ [1.18, if patient is African-American]

Abbreviated MDRD study equation ($ml/min/1.73m^2$):

$GFR = 186 \times [Scr]^{-1.154} \times [Age]^{-0.203}$ [0.742, if female]

$\times$ [1.210, if patient is African-American]

- Among adults, the MDRD Study equation provides a clinically useful estimate of GFR (up to ~ 90 mL/min/1.73 m^2)
- The MDRD Study equation derived based on:
  - GFR measured directly by urinary clearance of 125I-Iothalamate;
  - A large sample of >500 individuals with a wide range of kidney diseases;
  - Inclusion of both European-American and African-American participants;
  - Validated in a large (n > 500) separate group of individuals
- This equation provides estimates of GFR standardized for BSA.

- The abbreviated version (***J Am Soc Nephrol.* 2000;11: A0828**) requires only serum creatinine, age, sex, and race.
- Basic metabolic panel at UKCMC uses the abbreviated equation to report GFR.
- Per National Kidney Foundation recommendations: "*Nonetheless, questions remain about the equation's generalizability because it has not been validated in diabetic kidney disease, in patients with serious comorbid conditions, in normal persons, or in persons older than 70 years of age. Clinical conditions in which it may be necessary to measure GFR by using clearance methods include extremes of age and body size, severe malnutrition or obesity, diseases of skeletal muscle, paraplegia or quadriplegia, vegetarian diet, rapidly changing kidney function, and calculation of the dose of potentially toxic drugs that are excreted by the kidneys."* Many of these limitations also apply to the use of Cockcroft-Gault.
- Please note there are not sufficient studies to date that use the MDRD equation for adjusting drug dosages for patients with renal insufficiency. This may change in the near future as more studies with the MDRD equation are published.

Estimation of Clcr in Pediatrics:

$$\text{Clcr (infants up to 1 year of age, mL/min/1.73m}^2\text{)} = \frac{0.45 \times \text{Ht (cm)}}{\text{Scr}}$$

$$\text{Clcr (children 1 to 10 years of age, mL/min/1.73m}^2\text{)} = \frac{0.55 \times \text{Ht (cm)}}{\text{Scr}}$$

References: Schwartz GJ et al. J Pediatr. 1984;104:849-54 and Pediatrics. 1976;58:259-63.

AMINOGLYCOSIDES - CONVENTIONAL DOSING

1. Time of Sampling (*$132*)

   a. Relative to Dose

   - C_{pk} at 30 min after end of 30 min infusion (IV); 1 hr after injection (IM)
   - C_{tr} within 30 min prior to dose
   - at ss (4 to 5 estimated half-lives; normal renal function: t½ = 2-3 hrs) usually around 3rd maintenance dose (or later) preferably during day

2. Recommended Frequency of Sampling

   a. Routine Use In "Uncomplicated" Patients

   - initial C_{pk} and C_{tr}
   - repeat C_{pk} and C_{tr}, at new steady state, if initial values differ $\geq$ 25% from predicted (i.e. suggestive of unusual kinetic parameters or deviation from sampling guidelines)
   - Scr and BUN at least 2x/week; monitor other signs of renal function
   - repeat C_{pk} and C_{tr} q 1-2 wks, when duration of therapy $\geq$ 2 wks

   b. Use in “Complicated” patients (e.g., diminished or changing hydration status and/or renal function, concurrent ototoxic or nephrotoxic drugs)

   - initial C_{pk} and C_{tr} at steady state
   - Scr and BUN daily
   - repeat C_{pk} and C_{tr} weekly (or more frequently as dictated by clinical condition).

3. Therapeutic Range (Conventional Dosing)*

Patients with normal renal function*: Conventional dosing for gentamicin and tobramycin ~1-2 mg/kg-DBW/dose q8hrs and amikacin ~5mg/kg-DBW/dose q8hrs. NOTE*: Elderly patients often require a g12hr or longer dosing interval.

- Primarily used as double coverage or synergy with β-lactams for aerobic gram-negative infections (e.g. *Pseudomonas, Enterobacter, Proteus, E. coli, Serratia*)

- Can be used for synergy with some gram-positive infections (e.g. *Enterococcus, Staphylococcus*)

Concentration	gentamicin, tobramycin	amikacin
C_{pk} (mg/L)	5 -10	25 - 35
C_{tr} (mg/L)	0.5 - 2	4 - 10

***Desired C_{pk} and C_{tr} concentrations for conventional aminoglycoside dosing should be determined clinically by site and severity of infection, causative organism and its MIC, immunocompetence of patient, intent of therapy, etc.**

See table below for general recommendations for desired C_{pk} based on type of infection. *Final decision for desired concentrations should be based on clinical outcomes in addition to a pharmacokinetic assessment.

Types of infections*	**Suggested Target Peak Concentrations (mg/L) (gentamicin or tobramycin)**
Abdominal infections	6-8
Bacteremia	6-8
Empiric therapy in cystic fibrosis	8-12
Endocarditis, Bacterial (prevention & treatment) gram positive (*synergy: 1mg/kg/q8hrs)* gram negative	 3-5 8-10
Eye infections	6-8
Meningitis	8-10
Neutropenic patients	6-10
Peritonitis	6-8
Pneumonia	8-10
Skin and soft tissue infections	6-8
Urinary tract infections	4-6

4. General Guidelines for Monitoring

a. Initial Dosing

1. Select desired C_{pk} and C_{tr} based on site and severity of infection, causative organism and MIC, immunocompetence of patient, intent of therapy.

2. Estimate Cl_{cr}; standardize Cl_{cr} to 1.73 m^2 if BSA known:

$$Cl_{cr\,(std)} = Cl_{cr} \times \frac{1.73 m^2}{\text{actual BSA}}$$

For obese patients use DBW = [IBW + 0.4 (TBW-IBW)] in the Cockcroft-Gault equation to estimate Clcr and standardize to 1.73m^2 to estimate aminoglycoside K. (Leader WG, Tsubaki T, Chandler MHH. Am J Hosp Pharm 1994; 51:2125-30)

3. Estimate K:

$$K = 0.00293 * Cl_{cr(std)} + 0.014$$

4. Estimate t½:

$$t½ = \frac{0.693}{K}$$

5. Estimate Vd*:

Vd = 0.25 L/Kg, average
Vd = 0.20 L/Kg, if dehydrated
Vd = 0.30 L/Kg, with CHF, volume overload, ICU patients

***Use ABW unless patient is obese (>125% IBW or TBW/IBW > 1.25)**
If obese use dosing body weight: DBW = IBW + 0.4 (TBW-IBW)

6. Calculate dosing interval (τ) :

$$\tau = \frac{\ln(C_{pk}/C_{tr})}{K} + t + T$$

t = infusion time (e.g., 0.5hr)

T = time between end of infusion & C_{pk} (e.g., 0.5hr)

7. Calculate maintenance dose (K_o) using target C_{pk}:

$$K_o = \frac{C_{pk}^{ss} \cdot Vd \cdot K \cdot (1\text{-}e^{-K\tau})}{(1 - e^{-Kt}) \cdot e^{-KT}}$$

t = infusion time (e.g., 0.5hr)

T = time between end of infusion & C_{pk} (e.g., 0.5hr)

****NOTE that K_o = mg/HOUR and the dose must be adjusted to account for 0.5hr infusion. (e.g. If K_o = 200mg/HR, then the dose = 100mg/30min for ½ hr infusion)**

8. Round dose to nearest 10mg or available stock bag dose (e.g., 80,100,120mg) then recalculate the actual C_{pk}:

$$\text{desired } C_{pk} \text{ X } \frac{\text{actual (rounded) dose}}{\text{calculated dose}} = \text{actual } C_{pk}$$

9. Estimate trough: $C_{tr}^{ss} = C_{pk}^{ss} \cdot e^{-KT'}$

   T' = time between C_{pk} and C_{tr}

10. *If necessary*, calculate loading dose (K_o*):

$$K_o^* = \frac{K_o}{(1\text{-}e^{\text{-}K\tau})} \quad \text{or} \quad = \frac{C_{pk} \cdot V \cdot K}{(1 - e^{\text{-}Kt})} \quad \text{or} \quad = V \cdot C_{pk}^{ss}$$

Weight-based method: 1.5 to 2 mg/kg (use DBW if obese)

b. <u>Dosage Adjustment Using Sawchuk-Zaske Method:</u>

Assumptions: Concentrations represent steady-state conditions; 1-compartment model; principle of superposition; linear elimination.

1. Verify administration and sampling times.

2. Calculate K:

$$K = \frac{\ln\left(\frac{C_{pk}^{ss}}{C_{tr}^{ss}}\right)}{T'}$$

T' is determined by subtracting the time difference between Cpk and Ctr from the Tau. For example, if the time difference between Cpk and Ctr was 1.5hrs and the Tau = q8hrs, then T' = (8 - 1.5) = 6.5hrs.

3. Calculate t½:

$$t½ = \frac{0.693}{K}$$

4. IF peak concentration is drawn late, calculate if drawn at correct time:

$$C_{pk}^{ss} = \frac{C_{pk}}{e^{\text{-}Kt'}}$$

where C_{pk}^{ss} = peak concentration drawn at appropriate time;

C_{pk} = peak concentration drawn late; t' = time between late C_{pk} and C_{pk}^{ss}

5. IF trough concentration is drawn early (e.g., >30min prior to dose), calculate if drawn at correct time:

   $C_{tr}^{ss} = C_{tr} * e^{-Kt'}$

   where C_{tr}^{ss} = trough concentration drawn at appropriate time

   (e.g., suggest use dose administration time)

   C_{tr} = trough concentration drawn early; t' = time between early C_{tr} and C_{tr}^{ss}

6. Calculate Vd:

   If doses have reached **steady state** (e.g., previous doses on time, concentrations drawn appropriately), use:

$$Vd = \frac{K_o(1-e^{-Kt})\,e^{-KT}}{C_{pk}^{ss} \cdot K\,(1-e^{-K\tau})}$$

   t = infusion time (e.g., 0.5hr)

   T = time between end of infusion & C_{pk}^{ss} (e.g., 0.5hr)

   If doses have **NOT** reached **steady state <u>AND</u>** there are at least 3 concentrations after a multiple dose (e.g., trough, peak, & random) or 2 concentrations after the 1st dose (e.g., peak and random or 2 random concentrations) use:

$$Vd = \frac{K_o(1-e^{-Kt})}{K\,(C_{pk}^{max} - C_{tr}e^{-Kt'})}$$

   C_{pk}^{max} = peak extrapolated to END of infusion

   t = time of infusion

   t' = time between C_{tr} and C_{pk}^{max}

   To use above equation, calculate peak at end of infusion:

$$C_{pk}^{max} = \frac{C_{pk}}{e^{-KT}}$$

   T = time between C_{pk} and C_{pk}^{max}

7. IF measured C_{tr} is high, calculate time required to achieve desired C_{tr}:

$$t' = \frac{\ln\left(Ctr_1 / Ctr_2\right)}{K}$$

   Ctr_1 = high Ctr; Ctr_2 = desired Ctr

   t' = time required from Ctr_1 to Ctr_2

8. Calculate new dosing interval (τ):

$$\tau = \frac{\ln(C_{pk}/C_{tr})}{K} + t + T$$

   t = infusion time (e.g., 0.5hr)

   T = time between end of infusion & C_{pk} (e.g., 0.5hr)

9. Calculate new dosing rate:

$$K_o = \frac{C_{pk}^{ss}\ Vd\ K(1-e^{-K\tau})}{(1-e^{-Kt})\ e^{-KT}}$$

t = infusion time (e.g., 0.5hr)

T = time between end of infusion & C_{pk} (e.g., 0.5hr)

NOTE that K_o = mg/HOUR and the dose must be adjusted to account for ½ HOUR infusion. (e.g. If K_o = 200mg/HR, then the dose = 100mg/30min for ½ hr infusion)

10. Round dose to nearest 10mg or available stock bag dose (80,100,120mg) then recalculate the actual C_{pk}:

$$\text{desired } C_{pk}\ X\ \frac{\text{actual (rounded) dose}}{\text{calculated dose}} = \text{actual } C_{pk}$$

11. Estimate trough to be obtained with above K_o and τ:

$$C_{tr}^{ss} = C_{pk}^{ss} e^{-KT'}$$

12. Document the pharmacokinetic assessment in the medical records.

    Document pertinent clinical monitoring parameters, dose recommendations and estimated and/or calculated pharmacokinetic parameters in the medical record. (*Also refer to Department of Pharmacy Guidelines for Writing Notes in Patient Charts, PH-02-04*)

    - Briefly describe the rationale of the drug and determine if warranted based on clinical and patient information.
    - Document the current day of therapy and goal length of therapy (e.g., Day #2/10 gentamicin), and any concomitant antibiotics.
    - Document the collect times of the reported concentrations and note if the samples were obtained appropriately. For example, if actual C_{pk} was drawn late, <u>also</u> document the estimated C_{pk} if drawn correctly.
    - Include the calculate PK parameters: K (hr^{-1}), t½ (hrs), Vd (L) <u>and</u> Vd (L/kg – DBW).
    - Write a new dosage in mg and mg/kg-DBW/dose (e.g., gentamicin 100 mg IV q8hrs, 1.5mg/kg/dose).
    - When changing a dosage, include the start time of new dosing regimen with the order (*very helpful for the pharmacist entering the order and the nurse administering the drug*).
    - Include a range for the predicted concentrations with the new dosage recommendation: (e.g., C_{pk} = 8-10mg/L; C_{tr} <2mg/L, ~1mg/L).
    - Include other pertinent information used to assess the patient: weight (ABW, IBW, DBW), height, BSA, Scr, Clcr, BUN, urine output, I/Os, cultures, Tmax, WBC, differential, allergies, and other nephrotoxic medications (e.g., furosemide, amphotericin, vancomycin).
    - Sample note provided on next page.

Sample Note

PHYSICAL / HISTORY / PROGRESS NOTES

Patient Name:
Medical Record:
Date of Birth:

Date	Clinical Pharmacokinetics Service RE: Tobramycin Day #2/14
9/2/2001 12:00 ABW = 90kg Ht = 6'0" IBW = 77.6kg DBW = 82.6kg BSA = 2.13m^2 Scr = 1.2 (today) Clcr = 86ml/min Clcr (std) = 70ml/min/1.73m^2	Patient is 50yo WM being treated with tobramycin 120mg IV q8hrs (1.45 mg/kg/dose) and Zosyn 3.375gm IV q6hrs for nosocomial pneumonia based on positive sputum cultures for *Pseudomonas aeruginosa*. Current Tmax 102.5, WBC = 15K. Tobramycin concs drawn around 3rd dose on 9/2: Trough = 2.2 mg/L C: 07:30 Dose = 120 mg IV infused from 08:00 – 08:30 Peak = 7 mg/L C: 09:00 Assessment of concs: Previous doses administered on time & represent steady-state; Ctr & Cpk drawn appropriately; Cpk is below recommended range for pneumonia (8-10mg/L) & Ctr above therapeutic range (<2mg/L). Renal function stable. PK parameters: K = 0.18hr^{-1}; t½ = 3.9 hrs; Vd = 19.6L (0.24 L/kg) Recommendations: 1. Suggest changing tobramycin to 160mg IV q12hrs (1.9 mg/kg/dose) to yield a Cpk ~8-10 mg/L & Ctr ~ 1mg/L; begin next dose at 20:00 today when conc. = 1mg/L; discussed with resident on primary team. 2. Not necessary to recheck Cpk & Ctr unless change in clinical status or renal function; if continue therapy > 7 days, would suggest recheck concentrations to assess for drug accumulation. 3. Suggest checking Scr/BUN at least 2X/week to assess renal function. George Davis, Pharm.D. #1740

Pediatric Guidelines (gentamicin, tobramycin):

Neonatal dosing guidelines (gentamicin, tobramycin) Assume Vd (0.5 - 0.6 L/kg)		
Gestational age	***Dosage***	***Comments***
< 34 weeks	4 mg/kg q24hrs	✓ Don't confuse "once daily" dosing with every 24-hour dosing interval in neonates. ✓ Neonates require a longer dosing interval (decreased clearance) and larger mg/kg dose (increased volume). ✓ Concentrations may not be warranted in all neonatal patients. ✓ If extended therapy is indicated (e.g., positive blood culture), concentrations (peak and trough) should be obtained with the 3rd dose. ✓ If urine output decreases < 1ml/kg/hr for at least 8 hours, concentrations are warranted. ✓ Goal concentrations usually: peak = 5-8mg/L; trough < 2mg/L. ✓ Dose may be infused over 20 minutes (always check administration technique as possible source of error).
≥ 34 weeks … <2 months postconceptional age	4 mg/kg q24hrs	

Infant and children dosing guidelines (gentamicin, tobramycin) *Assume Vd (0.3 - 0.35 L/kg)*	
Age	***Dosage***
Infants: ≥2 months <10 years	*7.5 mg/kg/day IV **divided** q8hrs* or 2.5mg/kg/dose IV q8hrs
Children: ≥10 –14 years	5 – 7.5 mg/kg/day IV **divided** q8hrs or 1.67-2.5 mg/kg/dose IV q8hrs
Children: >14 years - adult	1-2 mg/kg/dose IV q8hrs

Pediatric cystic fibrosis (CF) patients dosing guidelines (gentamicin, tobramycin) Vd = 0.4 – 0.45 L/kg	
Dosage	***Comments***
10 mg/kg/day IV divided q8hrs (Initial dosing or minor disease) or 14 mg/kg/day IV divided q12hrs (Moderate to severe disease)	✓ Larger Vd (0.4-0.45 L/kg) due to decreased body fat and increased Cl due to increased GFR. ✓ Pedaitric CF patients are excluded from the once-daily aminoglycoside dosing but some patients may be receiving a "high dose regimen" twice a day. ✓ For CF patients, levels are usually obtained on the 3rd day rather than the 3rd dose to allow for rehydration. ✓ Concentrations should be obtained at 4 and 10 hours post dose if dosed q12h (12 hours may not be measurable). Peak and trough levels appropriate for q8h dosing. ✓ Usually require higher doses to achieve desired concentrations (Cpk 8-14 mg/L; Ctr < 1mg/L). ✓ Must be very cautious of nephrotoxicity and ototoxicity because of long term and recurrent use. ✓ Repeat concentrations are usually not obtained unless significant changes in dose are warranted (e.g., >30%), available concentrations are not reliable, or therapy is continued beyond 14 days.

6. Guidelines for Dosing in End Stage Renal Disease (ESRD)

- Defined as GFR < 15 ml/min or on renal replacement therapy (RRT)

Gentamicin and Tobramycin Dosing/Monitoring – Conventional IHD

Monitor based on duration of therapy

1. Serum concentrations not necessary in patients on therapy <3-5 days
2. Serum concentrations recommended in patients with culture positive infection or expected duration of therapy > 5 days.

Guidelines for Monitoring

1. Initial dosing
    a. Assume Vd – 0.3-0.35 L/kg
    b. Synergy dosing
        i. Loading dose 1.5-2 mg/kg (DBW)
        ii. Maintenance dose 1mg/kg (DBW) after each hemodialysis
    c. Moderate to severe infections (aggressive management)
        i. Loading dose 2-2.5 mg/kg (DBW)

Effect of hemodialysis

1. Removes approximately 50% (4 hour session)
2. Levels taken post dialysis are true troughs; levels taken prior to dialysis can be used during the 50% removal assumption.

Concentrations

1. Single drug level approach (synergy dosing)
    a. Most commonly utilized approach
    b. Pre-dialysis (random) concentration
    c. Extrapolate post-dialysis concentration (trough) by assuming 50% drug removal during a 4 hour dialysis session
    d. Target of trough < 2 mg/L to conserve remaining kidney function and minimize risk for ototoxicity.
2. Multiple drug level approach (aggressive management)
    a. Peak concentration drawn 2 hours after dose
    b. Pre-dialysis (random) concentration

Maintenance dosing (multiple drug levels)

1. Calculate $K_e$off IHD
    a. $K_e$off IHD = (Ln Cp1/Cp2)/t
        Cp1 = Peak concentration; Cp2 = Pre-dialysis (random)
        t = time between Cp1 and Cp2
2. Calculate half-life off IHD
    a. $t_{1/2} = 0.693/k_e$off IHD
    b. Extrapolate actual peak concentration
    c. Extrapolate post-dialysis concentration (trough) by assuming 50% drug removal during dialysis
3. Determine Vd
4. Calculate maintenance dose using desired peak concentration (C_{pk})
    a. $K_o = (C_{pk(des)} – C_{tr}) \times Vd$
    b. Typical dosing 1-1.8 mg/kg after each dialysis session

Dialysis factors that may lead to lower percentage of drug removed
1. Dialysis duration <2 hours
2. Blood flow reduced to <200 mL/min
3. Ultrafiltration only (no hemodialysis)
4. Less permeable dialyzers (filters) used
5. Patient is volume overloaded

Aminoglycoside Dosing/Monitoring – CRRT

Dosing recommendations for critically ill adults receiving CVVHD/CVVHDF*

	Infection with Gm positive bacteria	Infection with gram-negative bacteria	
Aminoglycoside	Synergy dosage	Loading dose	Maintenance dosage
Gentamicin	1 mg/kg q24-36h	3 mg/kg	2 mg/kg q24-48h
Tobramycin	Not applicable	3 mg/kg	2 mg/kg q24-48h
Amikacin	Not applicable	10 mg/kg	7.5 mg /kg q24-48h

Note: Use calculated dosing body weight. Target peak and trough levels vary depending on type of infection.
*Trotman RL et al. CID 2005;41:1159-66.

Guidelines for Monitoring
1. Typical dosing interval during CRRT is q24-48h
2. Synergy dosing yields target peaks of 3-4 mg/L
3. Higher target peaks require longer dosing intervals

Levels
1. Two random serum concentrations will be obtained 4 and 12 hours after completion of the 1st dose.
2. Determine appropriate maintenance dose based upon calculated PK parameters (**ensure CRRT uninterrupted between concentrations**)

Factors that may lead to changes in amount of drug removed
1. Changes in ultrafiltration rate
2. Dialysis interrupted (i.e. filter clotted, particularly overnight)
3. Alterations in existing renal function (ARF vs CRF)

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ONCE-DAILY AMINOGLYCOSIDE (ODA) DOSING

There are several studies suggesting that larger doses of aminoglycosides given once-daily are just as effective, and less toxic, than conventional dosing given three times a day. ODA regimens take advantage of concentration-dependent killing through the optimization of peak concentration / MIC ratios. In addition, there are potential cost savings for nursing, pharmacy, and laboratory personnel. The ODA policy has been used on the Trauma Surgery Service at the University of Kentucky Chandler Medical Center since 1993. This is also referred to as **HIGH-DOSE, EXTENDED-INTERVAL AMINOGLYCOSIDE DOSING.**

Inclusion Criteria: All patients ordered aminoglycosides for prophylaxis, empiric therapy, or documented infection. (Aminoglycosides are usually indicated as synergistic or adjunctive therapy with other antibiotics as double coverage for gram-negative infections).

Exclusion criteria:

1. Patients with ascites
2. Patients with burns on >20% of total body surface area
3. Pregnant patients
4. Patients on dialysis
5. Patients with gram positive bacterial endocarditis
6. Pediatric patients
7. Cystic fibrosis patients (Guidelines on page 33 for pediatric CF dosing and page 41 for adult CF dosing)

Initial Dose: Doses should be based on **DOSING BODY WEIGHT**, ideal body weight plus 40% of estimated adipose tissue mass (*see Dosing Guidelines).*

Patients with estimated Clcr $\geq$ 40 mL/min/1.73m^2 will receive initial gentamicin dose of 7 mg/kg-DBW, infused over 30 minutes. Exceptions include Orthopedic Surgery services which commonly use 5mg/kg-DBW for prophylaxis/pre-emptive therapy with open fractures and Obstetrics services which use 5mg/kg -post-partum dosing body weight (see page 42 for OB guidelines).

Patients with estimated creatinine clearances < 40 mL/min/1.73m will receive an initial gentamicin dose of 3 mg/kg, infused over 30 minutes.

Monitoring: <u>Two concentrations (ordered as "random" concentrations)</u> will be obtained:

1) ***<u>1st</u>* <u>concentration</u>** will be drawn ~***<u>4 hours</u>*** after completion of the ***<u>1st dose</u>***.

NOTE: The random concentration at **4 hours post-infusion** may **range from 4-13 mg/L** depending on renal function and volume status. Patients with normal renal function (>100 ml/min) usually average a **4-hour random ~5-8 mg/L** (*see mean concentration-time curve on page 41).*

The rationale for obtaining a "4-hour" sample versus a "peak" is to determine the serum concentration after the distribution phase. A prolonged distribution phase has been described in trauma patients (Jennings HR, et al. *Pharmacotherapy*. 2000;20(10):1265) and healthy volunteers (McNamara DR, et al. *J Clin Pharmacol* 2001 Apr;41(4):374-7) who received 7 mg/kg. Post-distribution concentrations provide a more accurate calculation of elimination rate and the estimation of the 24-hour concentration.

2) ***<u>2nd</u>* <u>concentration</u>** will be drawn ~***<u>12 hours</u>*** after completion of the ***<u>1st</u>* <u>dose</u>**.

NOTE: The concentration at **12 hours post-infusion** will vary depending on renal function. The **12-hour concentration** may be **<1 mg/L in patients with normal renal function.**

Patients with normal renal function should have a prolonged "drug-free" period. ODA therapy should usually NOT be used as the single antibiotic agent and patients should not receive a dose of 7mg/kg more frequently than once every 24 hours until more studies are available. Some patients may warrant conventional dosing to maintain concentrations. Please consult the Clinical Pharmacokinetic Service (257-8403) or ID service regarding any concerns about ODA therapy or patient eligibility.

Subsequent Doses: The goal of the initial concentrations after the 1st dose is to verify that the drug is eliminated appropriately before the 2nd dose and to establish the dosing interval. Subsequent doses will be the same as the initial dose, but the dosing intervals will be adjusted to achieve troughs **< 1 mg/L.** Appropriate dosing intervals include every 24, 36, or 48 hours. Scr/BUN should be measured at baseline and 2X/week thereafter.

- **Patients with normal renal function will usually have a "drug-free" period with an undetectable trough concentration < 0.3 mg/L.**
- **For patients with trough concentration > 0.3 mg/L, renal function should be monitored closely and risks of nephrotoxicity and ototoxicity evaluated carefully.**
- **If the serum concentration following a 7mg/kg dose requires > 48 hours to decline to <1mg/L, then 3mg/kg or conventional dosing may be warranted.**
- **Patients should not receive a single dose of 7mg/kg more frequently than every 24 hours until more studies are available.**

Follow-up monitoring: If ODA therapy is continued for > 7days, a trough concentration should be obtained weekly to check for drug accumulation and assess risk of nephrotoxicity. Scr/BUN should also be monitored at least 2X/week to assess any changes in renal function and risk of nephrotoxicity. Concomitant nephrotoxic drugs should be avoided if possible.

Ototoxicity should be monitored closely. Ototoxicity results from damage to the vestibular and cochlear portions of the eighth cranial nerve. **Auditory symptoms include tinnitus, roaring, ringing, or "buzzing" in the ears, and varying degrees of hearing impairment**. Loss of high-frequency perception is only detectable by audiometric testing and usually occurs before clinical hearing loss. **Vestibular symptoms include nausea, vomiting, dizziness, vertigo, nystagmus, oscillopsia, and ataxia. A feeling of fullness in the ears and tinnitus are early signs of ototoxicity. Symptoms are exacerbated in the dark.** Hearing loss may be irreversible, but patients usually retain normal conversational hearing. Other ototoxic drugs (e.g., lasix) should be avoided if possible.

INITIAL DOSING GUIDELINES FOR ADULTS:

1. Estimate Creatinine Clearance (Cl_{cr}) using Actual Body Weight (ABW) for non-obese patients; in obese patients (*>125% IBW*) use Dosing Body Weight (see below for equation).

   Males $Cl_{cr} = \frac{(140\text{-Age}) \times ABW}{72 \times Scr}$ Females $Cl_{cr} = Cl_{cr} * 0.85$

2. Estimate Body Surface Area (BSA) using the Mosteller equation:

   $$BSA\ (m^2) = \frac{\sqrt{Ht(cm)\ x\ Wt(kg)}}{60}$$

3. Calculate Standardized Creatinine Clearance:

   $$Cl_{cr(Std)} = Cl_{cr} * \frac{1.73 m^2}{BSA}$$

4. Determine Ideal Body Weight (IBW).

   IBW (kg) = 50 (kg) + (2.3 (kg) x ea. inch over 5 ft) male
   = 45 (kg) + (2.3 (kg) x ea. inch over 5 ft) female

5. Calculate Dosing Body Weight (DBW):

   DBW = IBW + 0.4 (ABW-IBW) *(If ABW<IBW, then DBW = ABW)*

6. Calculate the patient's dose (**gentamicin & tobramycin**) based on Dosing Body Weight.

   a) If **$Clcr_{(std)} \geq$ 40 ml/min/1.73m^2**, then give **7 mg/kg-DBW**.

   b) If **$Clcr_{(std)} <$ 40 ml/min/1.73m^2**, then give **3 mg/kg-DBW**.

   Amikacin: Doses used for single daily administration of amikacin range from 15 to 20 mg/kg/day (Marik et al, 1991; Maller et al, 1993 - 20mg/kg/dose: Cpk ~40mg/L and Ctr_{24hr} <4mg/L).

7. Dilute dose in 100 ml of either 5% Dextrose or Normal Saline and infuse over 30 minutes.

8. Order two concentrations at 4 and 12 hours after the end of 1st dose.

CALCULATE PARAMETERS:

1) Calculate K:

$$K = \frac{\ln\left(C1_{random} / C2_{random}\right)}{T'}$$

$C1_{random}$ = 1st random ~4hrs after dose
$C2_{random}$ = 2nd random ~12 hrs after dose
T' = time between $C1_{random}$ and $C2_{random}$

2) Calculate C_{pk} at 0.5hr after 1st dose (30-min infusion):

$$C_{pk}^{0.5hr} = \frac{C1_{random}}{e^{-KT'}}$$

T' = time between $C1_{random}$ and $C_{pk}^{0.5hr}$

3) Calculate C_{tr} at 24 hours:

$$C_{tr}^{24hr} = C_{pk}^{0.5hr} * e^{-K*23}$$

If 24hr $C_{tr} \leq$ 1 mg/L continue q24hr dosing
If 24hr C_{tr} > 1 mg/L extend dosing interval

4) Calculate V using C_{pk}^{max} (peak extrapolated to the END of infusion)

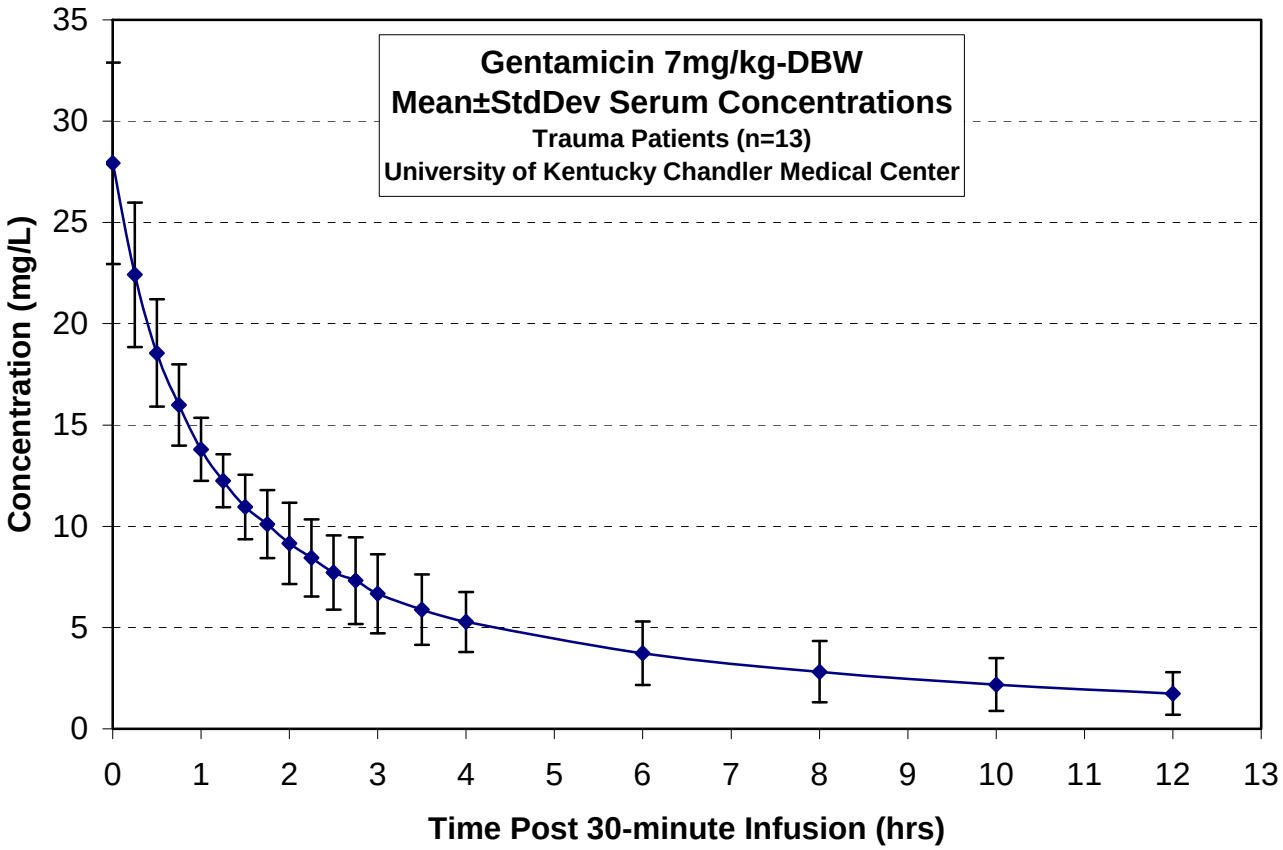
$$C_{pk}^{max} = \frac{C_{pk}^{0.5hr}}{e^{-Kt}}$$

t = 0.5hr (time between C_{pk}^{max} and $C_{pk}^{0.5hr}$)

$$V = \frac{K_o(1 - e^{-Kt})}{K(C_{pk}^{max})}$$

t = infusion time

If assistance is required in selecting patients or determining the proper dose or dosage interval, contact the pharmacist rounding with the service, the Clinical Pharmacokinetics Service (257-3378, UK beeper #1740), the Pharm.D. Resident on call (UK beeper #1875), or the Infectious Disease Service.



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ODA Dosing for Adult Cystic Fibrosis Patients:

Inclusion criteria:

- ✓ Adult patients 18-35 years of age
- ✓ Estimated Clcr > 60ml/min
- ✓ Must obtain baseline SCr in patients at increased risk of renal insufficiency
    - o History of renal dysfunction
    - o Diabetes mellitus

Dosing and monitoring recommendations (Tobramycin):

- ✓ 12 mg/kg (DBW) IV q24 hours
- ✓ Obtain 4 and 12 hour levels following infusion of **third** dose
    - o Goal Ctr < 0.5 mg/L
    - o If 12 hour concentration is <1 mg/L, consider increasing dose to 15 mg/kg/day or shorten dosing interval (i.e. 7-8 mg/kg IV q12h).
    - o If estimated (calculated) trough level prior to next dose (Ctr) is >0.5 mg/L, calculate new dose to achieve Ctr <0.5mg/L
- ✓ Repeat trough concentrations indicated if significant changes in dose occur or if therapy is to continue an additional 7 days
    - o Draw trough concentration once weekly, goal Ctr $\leq$0.5mg/L
    - o Assess renal function 2x weekly while patient on therapy

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2. Aminimanizani A, Beringer PM, Shapiro BJ et al. Distribution and elimination of tobramycin administered in single or multiple daily doses in adult patients with cystic fibrosis. J Antimicrob Chemother 2002; 50:553-9.
3. Beringer PM, Vinks AA, Shapiro BJ et al. Pharmacokinetics in adults with cystic fibrosis: Implications for once-daily administration. Antimicrob Agents Chemother 2000; 44(4):809-13.
4. Bates RD, Nahata MC, Barson WJ et al. Pharmacokinetics and safety of tobramycin after once-daily administration in patients with cystic fibrosis. Chest 1997; 112:1208-13.

ODA Dosing for Postpartum Endometritis

Indications:
- Postpartum endometritis
- Postpartum treatment of chorioamnionitis - *Prior to delivery, use conventional gentamicin dosing (e.g., 1-2 mg/kg/dose IV q8hrs); start once daily dosing 8 hours after conventional dose*

Inclusion criteria:
- Current postpartum weight
- Age ≥ 18 years old
- Normal renal function (serum creatinine < 1.4mg/dL) - *Must obtain baseline serum creatinine in patients with increased risk for renal insufficiency prior to receiving once daily gentamicin including:*
  - History of renal dysfunction
  - Diabetes mellitus
  - Preeclampsia
  - Toxemia

Dosing Recommendation:
1. Assess if patient is obese using height and postpartum weight - *Refer to table on next page to determine obesity*

2. If NOT obese, use ACTUAL postpartum body weight (PPABW):
   GENTAMICIN DOSAGE = 5mg/kg X PPABW IV q24hrs

3. If obese, use postpartum DOSING body weight (PPDBW):
   PPDBW = PPIBW + 0.4 (PPABW - PPIBW)

   GENTAMICIN DOSAGE = 5mg/kg X PPDBW IV q24hrs

Follow-up Monitoring:
- SERUM GENTAMICIN CONCENTRATIONS are NOT warranted unless the patient meets at least one of the following criteria:
  a. Increased risk for renal insufficiency (risk factors listed above)
  b. Duration of gentamicin therapy is continued for > 3 days
  c. Patient is not responding to antibiotic therapy

- If serum gentamicin concentrations are warranted (refer to list above):
  TWO GENTAMICIN CONCENTRATIONS should be obtained 4 AND 12 hours after the dose (order as "4 and 12 random gentamicin concentrations")
  - A pharmacist on the Clinical Pharmacokinetics Service (#1740) will assess the concentrations and calculate the gentamicin trough (goal: <1mg/L) and recommend a new dosage if necessary.
  - A pharmacy resident on-call (#1875) is also available after 5pm and weekends if necessary.

Additional monitoring:
- If duration of aminoglycoside therapy continues > 3 days, suggest checking a serum creatinine
- If duration of aminoglycoside therapy continues > 7 days, suggest checking follow-up gentamicin TROUGH CONCENTRATION to assess for potential accumulation

1. **PPIBW = postpartum ideal body weight: PPIBW (kg) = 54* + (2.3 X every inch in height over 5 feet).**

NOTE: PPIBW calculated by adding 9kg (20lbs) to normal ideal body weight.

Patient is considered obese if PPABW is >125% X PPIBW.

Height	PPIBW (kg)	PPABW considered to be obese [2] (kg)
4'10"	49	62
4'11"	52	65
5'0"	54	68
5'1"	56	70
5'2"	59	73
5'3"	61	76
5'4"	63	79
5'5"	66	82
5'6"	68	85
5'7"	70	88
5'8"	72	91
5'9"	75	93
5'10"	77	96
5'11"	79	99
6'0"	82	102
6'1"	84	105
6'2"	86	108
6'3"	89	111
6'4"	91	114
6'5"	93	116
6'6"	95	119

Other methods used for ODA dosing (*NOTE: This information is provided for comparison only, please refer to UKCMC approved protocol*):

Hartford Hospital Nomogram (Nicolau et al *Antimicrob Agents Chemother* 1995;39.)

- Dose = 7mg/kg IV q24hrs for Clcr > 60ml/min (also refer to table below)
- Interval based on nomogram using **SINGLE** random concentration between 6-14 hours
  - Computer simulated dosing nomogram
    - Designed to achieve Cpk ~20 mg/L
    - Tested with PK parameters of patients on conventional dosing regimens
    - Confirmed in patients (n=20) receiving 7 mg/kg
- Assumes one-compartment model
- Assumes 60 min distribution phase
- May not be accurate for doses less than 7mg/kg (e.g., 5mg/kg)

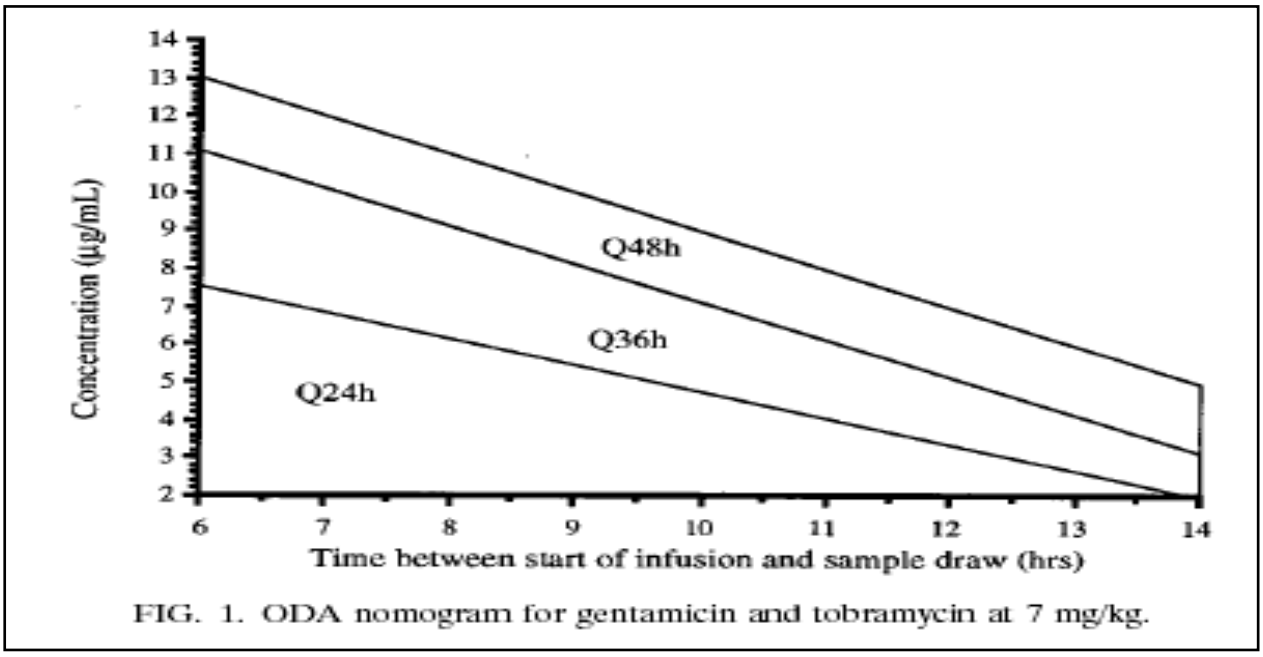


FIG. 1. ODA nomogram for gentamicin and tobramycin at 7 mg/kg.

Comparison of different methods:

Nomogram	Gentamicin Dose (mg/kg)	Dosing Interval (hrs)		
		Clcr ≥ 60 ml/min	Clcr 40-59 ml/min	Clcr 20-39 ml/min
Hartford Hospital*	7	24	36	48
Barnes-Jewish Hospital*	5	24	36	48
University of Rochester*	5	24	36	48
UKCMC	7	24	24	*Use 3mg/kg IV q24hrs*

*Source: *Pharmacotherapy*. 2002 Sep;22(9):1077-83.

Sanford Guide 2004 – Recommended Gentamicin/Tobramycin Dosing Regimen

Clcr (ml/min)	Dose (mg/kg)	Interval (hrs)
≥ 80	5.1 (7 if critically ill)	24
60-79	4.0	24
40-59	3.5	24
30-39	2.5	24
20-29	4.0	48
10-19	3.0	48
<10	2.0	48

AUC Method (*Br J Clin Pharmacol.* 1995 Jun;39(6):605-9.):

Clcr (ml/min)	Starting Dose (mg/kg)	Target AUC	Time of Second Sample
>66	5, 6, or 7	72, 86, 101	6-14 hr
54-66	5 or 6	86, 101	8-16 hr
42-53	5	101	10-18 hr
30-41	4	101	12-20 hr
21-29	3	101	14-22 hr
<21	Seek specialist advice		

- Administer dose over 30 minutes
- Take blood sample 30 minutes after end of infusion (Cpk)
- Take second blood sample within time frame indicated in table
- Calculate the patient's aminoglycoside AUC using:

$$AUC\ (0\text{-}24hrs) = 1.065\ (\frac{C_{end\ of\ infusion} - C_{24}}{K})$$

- Calculate 2nd dose:

$$Dose\ 2 = \frac{AUC_{target}}{AUC_{observed}}\ X\ Dose\ 1$$

- Administer 2nd dose 24hrs after the first dose
- Monitor as above every 48hrs or according to the patient's clinical condition

CARBAMAZEPINE

1. Time of Sampling (*$114*)

   a. Relative to Dose

   - trough within 1 hour prior to dose
   - at ss

2. Recommended Frequency of Sampling

   a. Initially after reaching steady-state (2 to 10 days of chronic dosing); "true" steady-state may not be reached for several weeks, due to autoinduction, which results in increasing clearance. Induction begins within 3 to 4 days of therapy and is maximal after 3 to 4 weeks.

   b. After each dosage adjustment at ss.

3. Therapeutic Range

   4 – 12 µg/ml (8-12 µg/ml reported by UKCMC TDM Lab)

   1.4 – 3.5 µg/ml (**saliva**)

   Note: Carbamazepine used as single anticonvulsant therapy may require higher serum concentrations than when used in a multiple anticonvulsant regimen.

4. General Guidelines for Monitoring

   a. Initial Dosing

Empiric	- epilepsy	200 mg PO BID
	- trigeminal neuralgia	100 mg PO BID

   b. Maintenance Dose

   - Increase dose by 100-200 mg/day every week
   - Based on initial level and response to therapy, dosage may have to be gradually increased during the first few weeks, due to autoinduction.
   - Final maintenance dose is usually:
     - epilepsy 10-20 mg/kg/day
     - trigeminal neuralgia 3-20 mg/kg/day
   - Best to give in divided doses, usually q 12^{o} (or q 8^{o}), rather than in a single daily dose.
   - Dosing best at mealtime.
   - Maximum dose - usually 1200 mg/day

c. Dosage Adjustment

The $\bar{c}$ equation may be used once "true" steady-state is achieved.

$$\bar{c} = \frac{S \times F \times X_o}{Cl_s \times \tau}$$ S = 1; F = 0.7-1.0 (Tegretol)

d. Available products at UK Hospital

Tegretol® 200mg tablets, 100mg chew tabs, 100mg/5ml suspension

5. Pediatric Guidelines

- Should not be used in infants < 1 yo (although package insert states < 6 yo)
- Initial dose - 10 mg/kg/day
- Maintenance dose - 20-60 mg/kg/day (gradually increase from initial dose)
- Also see #9 - Miscellaneous

6. Other Monitoring Guidelines

- Baseline CBC
- CBC every month (x 2), then every 6 months after stabilized

7. Drug Interactions

- CBZ induces its own metabolism (P450 3A4) during prolonged treatment, and is complete 3 to 5 weeks with a fixed dosing regimen (Prod Info Tegretol(R), 1998).
- *Active metabolite: carbamazepine-10,11-epoxide*
- Since CBZ is an enzyme inducer of many P450 enzymes (3A4, 2D6, 2C), it may enhance the elimination of other drugs (e.g. ethosuximide, warfarin, and benzodiazepines that undergo hydroxylation).
- Enzyme inhibitors may increase CBZ levels (e.g. cimetidine, erythromycin, isoniazid, propoxyphene, and verapamil)
- Phenytoin - CBZ interaction is variable. Phenytoin levels may increase, decrease, or stay the same. CBZ levels usually decrease.

8. Adult Pharmacokinetic Parameters

- Vd = 1.4 ± 0.4 L/kg
- Cl = 1.3 ± 0.5 ml/min/kg (multiple dosing)
  = 0.4 ± 0.1 ml/min/kg (single dose)
- t½ = 15 ± 5 hours (multiple dosing)
  = 36 ± 5 hours (single dose)

9. Miscellaneous

- Absorption is variable, depending on factors such as presence of food and product formulation (recommend not using generics - only Tegretol®).
- Patients with severe renal failure (Cl_{cr} < 10 ml/min) should receive only 75% of the usual daily maintenance dose.
- Protein binding is approximately 70% (binds to both albumin and α-1 AGP).

10. Suggested References

General:

Bertilson (1978) Clin Pharmacokin 3:128.

Drug Interactions:

Phenytoin Zielinski (1985) Ther Drug Monit 7:51.
Zielinski (1987) Ther Drug Monit 9:21.

Verapamil Macphee (1986) Lancet 1:700.

DIGOXIN

1. Time of Sampling (*$70*)

   a. Relative to Dose

   - Drug concs should be drawn during the post-absorptive, post-distributive phase of drug elimination, ie, during the 6 to 24 hour interval following the previous dose
   - Prefer trough within 1h prior to dose
   - At ss (usually 5-7 days; if normal renal/hepatic fx: t½ = 36 ± 8hrs, adults)

2. Recommended Frequency of Sampling

   a. Routine Use in "Uncomplicated" Patients

   - Initial level at ss

   b. Use in Unstable Patients

   - Initial level at ss
   - Repeat level every 5 to 7 days, or as dictated by a change in concurrent disease state/drug therapy, lack of adequate response to a previously adequate dose, or occurrence of adverse effects attributable to digoxin.

3. Therapeutic Range**

   UK: 0.8-2.0 ng/ml (conversion note: 1ng/ml = 1µg/L)

   CHF: *0.5-1.0 ng/ml*
   Pharmacotherapy.1999 Oct; 19(10): 1123-6.

   Arrhythmias: may require higher concs for atrial fibrillation

   ** *Establishment of a true therapeutic range is complicated by effects of electrolyte imbalances and of assay interference by digoxin-like immunoreactive substances (DLIS) and digoxin metabolites. (see 4b. Dosing Adjustments)*

4. General Guidelines for Monitoring

a. Loading Dose

Rapid digitalization can typically be achieved utilizing loading doses of 8-12 mcg/kg LBW (normal renal function). Use LBW, since digoxin does not distribute appreciably into body fat.

$$X_o^* = \frac{C \times V}{S \times F}$$

S = 1
F = 0.7 (tablet)
= 0.8 - 0.85 (elixir; capsule)

V = 7.3 L/Kg in normal renal function**

** For patients with compromised renal function:

$$V_{(L/1.73m^2)} = 226 + \frac{298 * Cl_{cr}\ (\text{stdz to } 1.73m^2)}{29.1 + Cl_{cr}\ (\text{stdz to } 1.73m^2)}$$

$$\text{e.g. std } Cl_{cr} = Cl_{cr} * \frac{1.73m^2}{\text{actual BSA}}$$

$$V_{(L/70\ Kg)} = 269 + 3.12 * Cl_{cr}\ (\text{stdz to } 70\ Kg)$$

$$\text{e.g. std } Cl_{cr} = Cl_{cr} * \frac{70\ Kg}{\text{actual LBW (Kg)}}$$

The loading dose should be given in <u>divided</u> doses so that the patient can be evaluated for toxicity and efficacy prior to receiving total load. (e.g. usually give <u>1/2 of the calculated load initially</u>, followed by <u>1/4 in 6h and the remaining 1/4 in 6h after the second dose,</u> making sure to monitor the patient after each dose).

b. Maintenance Dose:

$$X_o(mcg) = \frac{\bar{c} \cdot Cl_s \cdot \tau}{F \cdot S}$$

(Helpful hint: use mcg/L for $\bar{c}$, 24hrs for τ, and L/hr for Cl)

For patients without HF:

Cl_s = 1.303 (Cl_{cr}, std to 1.73 m^2) + 40 ml/min/1.73 m^2 (ml/min/1.73m^2)

Patients with uncompensated HF (e.g. pitting edema, signs of hepatic congestion):

Cl_s = 1.303 (Cl_{cr}, std to 1.73m^2) + 20 ml/min/1.73m^2 (ml/min/1.73m^2)

c. Dosing Adjustments

Calculate actual Cl_s, based on $\bar{C}$ (level, usually obtained at τ), F, and X_o (dose administered).

$$Cl_s = \frac{S \cdot F \cdot X_o}{\bar{c} \cdot \tau}$$

Calculate new maintenance dose.

$$X_o = \frac{\bar{c} \cdot Cl_s \cdot \tau}{F \cdot S}$$

One should check if the therapeutic response to digoxin correlates well with the level(s) obtained, prior to making dosage adjustment(s). The failure of digoxin levels to correlate with therapeutic/toxic response is often due to aberrations in serum and tissue concentrations of sodium, potassium, magnesium, and calcium. Patients with low potassium, magnesium, or sodium levels or high calcium levels may be more sensitive to digoxin) or due to presence of DLIS in certain subpopulations (e.g. renal failure patients, combined renal and hepatic failure patients, pregnant women, neonates, infants).

d. Chart note

Monitoring parameters should include heart rate, ECG, serum electrolytes (K, Mg, Na, Ca), Scr, Clcr, interacting medications and monitoring for signs and symptoms of toxicity. PK parameters should include digoxin Cls in ml/min.

5. Factors Influencing Digoxin Pharmacokinetics/Pharmacodynamics

- Renal dysfunction, obesity, CHF (see 4a.)
- Hypothyroidism: ↓ digoxin Cl_s
- Hyperthyroidism: ↑ digoxin Cl_s
- Hypokalemia, hypomagnesemia, hypercalcemia: ↑ digoxin cardiac effects

- Drug interactions:
  - Drugs associated with ↓ digoxin absorption include: antacids, cholestyramine, colestipol, kaolin-pectin, metoclopramide, neomycin, sulfasalazine; ↑absorption *include: propantheline*.
  - Quinidine - ↓ digoxin Cl_s; multiply digoxin Cl_s by 0.5
  - Verapamil - ↓ digoxin Cl_s; multiply digoxin Cl_s by 0.7
  - Spironolactone - ↓ digoxin Cl_s; multiply digoxin Cl_s by 0.5
  - Amiodarone - ↓ digoxin Cl_s; multiply digoxin Cl_s by 0.7

6. Pediatric Guidelines

Dosage Recommendations for Digoxin[1, 2]

AGE	Total Digitalizing Dose* (mcg/kg)		Daily Maintenance Dose# (mcg/kg)	
	Oral	Intravenous	Oral	Intravenous
Preterm neonate	20-30	15-25	5-7.5	4-6
Full-term neonate	25-35	20-30	6-10	5-8
1 mo - 2 yrs	35-60	30-50	10-15	7.5-12
2 - 5 yrs	30-40	25-35	7.5-10	6-9
5 - 10 yrs	20-35	15-30	5-10	4-8
>10 yrs	10-15	8-12	2.5-5	2-3

Average Dosage Recommendations for Adults (mg)				
Adults	0.75-1.5mg	0.5-1mg	0.125-0.5mg	0.1-0.4mg

1. Bendayan R, McKenzie MW. Digoxin Pharmacokinetics and dosage requirements in pediatric patients. *Clin Pharm* 1983;2(3):224-35.

2. Park MK. Use of digoxin in infants and children with specific emphasis on dosage. *J Pediatr* 1986; (6): 871-7.

* Administer ½ of the total digitalizing dose in the initial dose, then ¼ of the total dose in each of two subsequent doses at 6-12 hour intervals. The doses are divided to allow sufficient time for distribution and maximum effect to assess for therapeutic response and potential toxicity after each dose.

\# Divided every 12 hours in infants and children < 10 years of age. Administered once daily for children > 10 years of age and adults.

e. Other Considerations

Vd: 6-20 L/kg *(caution: wide patient variability may be secondary to design problems in initial studies)*

- *DLIS (digoxin-like immunoreactive substance)*: very common in newborn infants.
- Serum concentrations may not be warranted in every patient.
- Digoxin therapy should first be evaluated based on response and toxicity versus measuring drug concentrations.

7. Dosage forms on UK formulary

Digoxin tablets 0.125mg, 0.125mg
Digoxin injection 500 mcg AMP/2ML; 250mcg TUBEX
Digoxin elixir 50 mcg/ml 60ml BTL; 250mcg 5ml TUB; 125mcg 2.5ml TUB

Digoxin injection (**PEDIATRIC STRENGTH**): 100 mcg/ml (1ml AMP);
Also 10mcg/ml *DILUTED*

8. Suggested References for Factors Influencing Digoxin Disposition

Applied Pharmacokinetics (2006), 4th ed., p. 410-439.
Renal dysfunction: Jusko (1974) J Clin Pharmacol 14:525-535.
Obesity: Ewy (1971) Circulation 44:810-814.
CHF: Koup (1975) Clin Pharmacol Ther 18:9-21.
Thyroid diseases: Ochs (1982) Clin Pharmacokinet 7:434-451.

Drug interactions:

Waldorff (1978) Clin Pharmacol Ther 24:162-167.
Klein (1980) New Engl J Med 303:160.
Pedersen (1981) Clin Pharmacol Ther 30:311-316.
Bigger (1981) Int J Cardiol 1:109-116.
Pedersen (1983) Eur J Clin Pharmacol 24:41-47.
Nademanee (1984) J Am Coll Cardiol 4:111-116.

Digoxin Immune Fab (DIGIBIND®, DIGIFAB®)

1. Indications

   a. Manifestations of severe toxicity: ventricular arrhythmias, progressive bradyarrhythmias, 2nd or 3rd degree heart block not responsive to atropine, refractory hypotension.

   b. Potassium concentration >5 mEq/L in patients with manifestations of severe cardiac glycoside toxicity

   c. Significant risk of cardiac arrest: ingestion of >10 mg in an adult, >4 mg in a child, level >10 ng/mL post-distribution (generally 6-8 hours postingestion), progressive increase in potassium level postingestion.

   d. Unresponsiveness to immediately available conventional therapy.

   e. Digoxin serum levels of >10 ng/mL by 6 hours after the overdose, even in asymptomatic patients, is considered an indication for digoxin immune FAB by some authors (Bailey et al, 1997).

2. Recommended dosing for adults

   NOTE: (Pharmacy acquisition c*ost ~$500/vial)*

   a. ***Acute ingestion of known amount:*** Each vial of Digoxin Immune Fab will bind approximately 0.5mg of digoxin (or digitoxin). Thus, one can calculate the total number of vials required by dividing the total digitalis body load by 0.5mg/vial:

$$\text{Dose (in \# of vials)} = \frac{\text{Total digitalis body load in mg}}{\text{0.5 mg of digitalis bound/vial}}$$

   b. ***Based on steady-state digoxin concentrations*** Adult dose estimate of Digoxin Immune Fab (in # of vials) is represented in the table below or can be estimated using the following equation:

$$\text{Dose (in \# of vials)} = \frac{\text{(Serum digoxin concentration in ng/ml)(weight in kg)}}{100}$$

Patient Weight (kg)	**Serum Digoxin Concentration @ Steady State (ng/ml)**						
	1	2	4	8	12	16	20
40	0.5V	1V	2V	3V	5V	7V	8V
60	0.5V	1V	3V	5V	7V	10V	12V
70	1V	2V	3V	6V	9V	11V	14V
80	1V	2V	3V	7V	10V	13V	16V
100	1V	2V	4V	8V	12V	16V	20V

V = vials

3. Total Serum Digoxin Levels After Digoxin Immune Fab Administration:

Purpose:

Total serum digoxin levels obtained immediately after administration are unreliable. The Fab fragments bind to free digoxin, causing tissue-bound digoxin to be released from receptors and subsequently bind to the Digoxin Immune Fab. Digoxin levels drawn within 72 hours (for patients with normal renal function) or 7 days (in patients with renal failure) of administration will be falsely elevated.

Policy regarding total serum digoxin levels:

a. The pharmacist will alert TDM lab when Digoxin Immune Fab is ordered for any patient in the hospital.

b. TDM lab will not measure total serum digoxin levels for a period of at least 72 hours following administration for patients with normal renal function.

c. TDM lab will not measure total serum digoxin levels for a period of at least 7 days following administration for patients with severely impaired renal function.

d. If a digoxin level is ordered within the above times, TDM lab will notify the Pharm.D. managing that service for assessment.

References

1. Allen NM., Dunham GD. Treatment of digitalis intoxication with emphasis on the clinical use of digoxin immune Fab. DICP The Annals of Pharmacotherapy; 24: 991-998, 1990.

2. Antman EM., Wenger TL Butler VP., Haber E, Smith TW. Treatment of 150 cases of life threatening digitalis intoxication with digoxin specific Fab antibody fragments. Circulation; 81: 6: 1744-1752, 1990.

3. Schaumann W., Neubert P., Smolarz A., Kinetics of the Fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. European Journal of Clinical Pharmacology; 30: 527-533, 1986.

4. Ujhelyi MR., Colucci RD., Cummings DM., Green PJ., Robert S, Vlasses PH, Zarowitz BJ., Monitoring serum digoxin immune Fab therapy. DICP, The Annals of Pharmacotherapy; 25: 1047-1049, 1991.

LIDOCAINE

1. Time of Sampling (*$39*)

   a. Relative to Dose

   - 2h after load or 6-12h after initiation of therapy without load (ie @ ss)
   - Send out lab, may take 2-3 days for results to be reported

2. Recommended Frequency of Sampling

   - when toxicity is suspected
   - when ventricular arrhythmias occur (or recur) despite lidocaine administration
   - patients with suspected cardiac or hepatic insufficiency may require intensive serum concentration monitoring

3. Therapeutic Range

   1.5 - 6.0 mcg/ml

4. General Guidelines for Monitoring

   a. Initial Dosing*

   - Load

     MULTIPLE-BOLUS REGIMEN:

     Initial 75-100 mg (1 mg/kg) bolus, followed by 50 mg in 5-10 min. One to two additional 50 mg bolus doses may be given in 5-10 min intervals thereafter if necessary.

   or

     RAPID-INFUSION METHOD:

     Initial 75-100 mg bolus (over 2 min) and loading infusion of 150-200 mg (over 20 to 25 min).

Maintenance Dose:

1-4 mg/min (15-50 μg/min/kg, recommended for patient of lighter bodyweight)

Mean Systemic Clearance and Recommended Infusion Rates for Selected Patient Populations

Population	Systemic clearance (ml/min/kg) Mean ± SD	Infusion rate (μg/kg/min) to achieve 3 μg/ml Mean (Range)	Infusion rate (mg/min/70kg) Mean (Range)
Normal	15.6±4.6	47 (33-61)	3.3 (2.3-4.3)
Congestive heart failure	5.5±1.7	17 (11-22)	1.2 (0.8-1.5)
Acute myocardial infarction**	9.1±2.0	27 (21-33)	1.9 (1.5-2.3)
Congestive heart failure plus acute myocardial infarction	6.3±1.4	19 (15-23)	1.3 (1.1-1.6)
Chronic liver disease	6.0±3.2	18 (8-27)	1.3 (0.6-1.9)
Renal disease	13.2±3.2	40 (30-49)	2.8 (2.1-3.4)
Propranolol co-administration	9.4±3.1	28 (19-38)	2.0 (1.3-2.7)

Applied Pharmacokinetics (1986), 2nd ed., p. 662.

* For obese patients, it has been suggested that loading doses be based on TBW and maintenance infusions be based on IBW. [Abernathy (1984) Am J Cardiol 53: 1183)].

** α-1 acid glycoprotein (AAG) concs are elevated in AMI patients. Plasma protein binding of lidocaine is also conc-dependent. Consequently, free concentrations may be more useful for monitoring therapy.

Dosing Adjustments: $\bar{c} = \frac{K_o}{Cl}$

5. Other Factors Which Influence Lidocaine Disposition (See Table above)

Cimetidine co-administration:
Empirically ↓ usual infusion rate by 25%. Feely (1982) Ann Intern Med 96:592.

Elderly patients:
Empirically ↓ usual infusion rate by 20-30%. Abernethy (1984) J Cardiovas Pharmacol 5:1093.

LITHIUM

1. Time of Sampling (*$29*)

   a. Relative to Dose

   - At least 12 hours after the previous evening's dose (obtain concentration at same time of day).
   - At steady state ~ 5 days; t½ ~24hrs with normal renal function.

2. Recommended Frequency of Sampling

   a. Routine Use in Stable Patients

   - Initial level (at steady-state)

   b. Use in Unstable Patients

   - Initial level (at estimated steady-state)
   - Subsequent levels are appropriate with changes in renal function, to assess compliance, addition of concurrent medications that may affect lithium disposition or to assess toxicity.

3. Therapeutic Range

   - 0.6 to 1.2 mmol/L (Flame Photometry at UKMC)
     (1 mmol/L Lithium equals 1 mEq/L; 300 mg lithium carbonate = 8.12 mEq Li)
   - Concentrations from 1.2 to 2.0 mmol/L may be warranted in patients with acute mania.
   - Greater than 2.0 mmol/L are considered toxic.

4. General Guideline for Monitoring

   a. Initial Dosing

   Use population parameters with C-bar equation using

   $Cl_s \approx 0.25 * Cl_{Cr}$ [L/hr]

   $V_d \approx 0.8$ L/kg; t½ ≈ 18 - 24 hours

b. Empiric Dosing

Usually 600 to 1200 mg/day in 3 to 4 divided doses for immediate release dosage forms (once or twice a day for sustained release formulations).

Initial dose for acute mania: 900-1800 mg/day

Single Point Methods

Cooper Nomogram

- 600mg test dose of lithium carbonate
- One lithium serum concentration 24 hours later
- Converts observed lithium concentration to dosage required to achieve a steady-state concentration of 0.6 – 1.2 mmol/L
- Lithium serum concentration must be zero before test dose administration

LITHIUM SERUM CONCENTRATION 24 HOURS AFTER TEST (mmol/L)	LITHIUM CARBONATE DOSAGE REQUIREMENT
< 0.05	1200mg TID (3600mg/d)
0.05 – 0.09	900mg TID (2700mg/d)
0.10 – 0.14	600mg TID (1800mg/d)
0.15 – 0.19	300mg QID (1200mg/d)
0.20 – 0.23	300mg TID (900mg/d)
0.24 – 0.30	300mg BID (600mg/d)
> 0.30	300mg QD (300mg/d)

Perry Nomogram

- 1200mg test dose of lithium carbonate
- One lithium serum concentration 24 hours later
- Converts observed lithium concentration to maintenance dosage for desired steady-state concentration
- If using in acutely manic patient, anticipate a decrease in lithium maintenance dose once patient starts sleeping due to decrease in lithium clearance

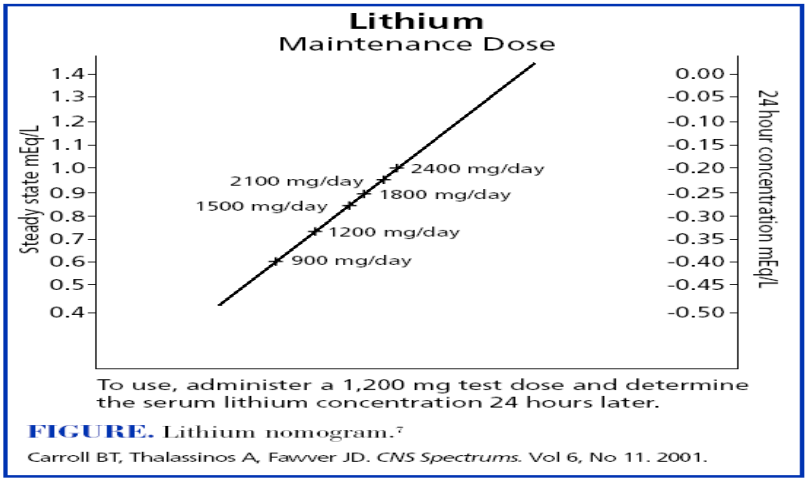


FIGURE. Lithium nomogram.[7]

Carroll BT, Thalassinos A, Fawver JD. *CNS Spectrums.* Vol 6, No 11. 2001.

Multiple-Point Method

Perry Method

- 600 – 1500mg test dose
- Two lithium serum concentrations 12 and 36 hours after the test dose
- Calculate elimination rate, half-life, accumulation factor, and so on
- Lithium serum concentration must be zero prior to test dose administration

c. Dosing Adjustments using steady-state concentration:

Calculate Lithium Clearance: $Cl_s = \frac{S \cdot F \cdot X_o}{C_{ss} \cdot \tau}$ F= ~1.0; S = 1.0

Recalculate Lithium dosing regimen: $X_o = \frac{C_{ss} * Cl_s * \tau}{S * F}$

5. Factors affecting Lithium concentration

Decrease	*Variable or no effect*	*Increase*
Acetazolamide Aminophylline Caffeine Osmotic diuretics Pregnancy* Sodium supplements	Amelioride Aspirin Furosemide Sulindac	ACE Inhibitors Ibuprofen Indomethacin Chronic lithium therapy Phenylbutazone Thiazides Dehydration Renal Impairment Sodium Loss Increasing age

* *Lithium clearance and serum concentrations return to pre-pregnant values after delivery.*

Patient Monitoring

MONITORING PARAMETERS	BASELINE	12 MONTHS	COMMENTS
Cardiac ECG Pulse and Blood Pressure	 * *		Patients older than 50 or those with preexisting cardiovascular disease; measure at baseline and every 6-12 months as indicated
Hematologic CBC with differential	 *	 *	
Metabolic/Endocrine Weight Serum electrolytes (Na, K, Ca, Phos) T_3, T_4, free thyroxine index, TSH	 * * *	 * * *	TSH is a better indicator of hypothyroidism and should be obtained every 3-6 months during maintenance therapy if thyroid function tests change, if TSH >4mIU/mL, or if symptoms of hypothyroidism occur.
Renal function Scr Urinalysis/osmolatity/specific gravity	 * *	 * *	Measure Scr in patients with impaired renal function; 24-hour Clcr indicated at baseline with hx of renal disease or abnormally high Scr or significant increases in Scr
Pregnancy Test In women of childbearing age	 *		
Plasma lithium concentrations			Measure every 1-3 months during maintenance therapy; every 5-7 days after any dosage change or possible drug interactions; less frequent monitoring in stable patients (every 6-12 months)

6. Products on UK Formulary

Lithium carbonate SR TAB 450MG
Lithium carbonate CAP 300MG
Lithium carbonate SR TAB 300MG
Lithium carbonate 300MG TAB
Lithium citrate LIQ 8MEQ/5ML 500ML

7. References

- Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring: © 1992 Third edition by Applied Therapeutics, Inc.
- Winter ME. Basic Clinical Pharmacokinetics. 1994 Third edition by Applied Therapeutics, Inc.
- Ward ME, Musa MN, Bailey Ll *J Clin Pharmacol.* 1994 Apr;34(4):280-5. Review.

METHOTREXATE

Rationale for kinetic monitoring ($76)

- Clinically relevant concentration-toxicity response
- Administration of an antidote
  - MTX is unique in that the administration of reduced folate compounds (leucovorin) will bypass the biochemical blockade and reverse the cellular damage

Absorption

- Incomplete & erratic absorption from GI tract
  - Highly variable absorption
    - n = 12 pediatric ALL F = 13-76%, DR=13-120mg/m^2)
  - **Dose-dependent absorption** (Michaelis-Menten pharmacokinetics)
    - ↑DOSE = ↓F
  - Generally at lower doses (≤ 25mg/m^2) F ~100% but still variable
    - Tmax = 1-5hrs, C_{max} = 0.25-1.25μM
  - Rate/extent of absorption affected by:
    - Food, oral nonabsorbable antibiotics, shortened intestinal time
- IM injection
  - Less variable, possible alternative if oral route problem

Distribution

- Very polar, requires active transport mechanisms to enter mammalian cells.
- Drug displays a bi or tri-exponential elimination curve resulting in a 2 or 3 compartment model
- Initial Vd ~ 0.2 L/kg
- Apparent Vd ~ 0.7 L/kg (variable, incr. w/higher concs. due to saturation of active transport system)
- Third spacing (e.g. by ascites or pleural effusion) creates a site of storage and "sustained release" of drug
  - Results in prolonged elevation of plasma concentrations and more severe toxicity and additional doses of antidote
- 50% bound to plasma proteins (albumin)
  - Potential drug interactions:
    - Sulfonamides
    - Salicylate
    - Chloramphenicol
    - Phenytoin
- CSF relatively impermeable, CSF concentrations 3% of plasma concentration; intrathecal administration is usually required

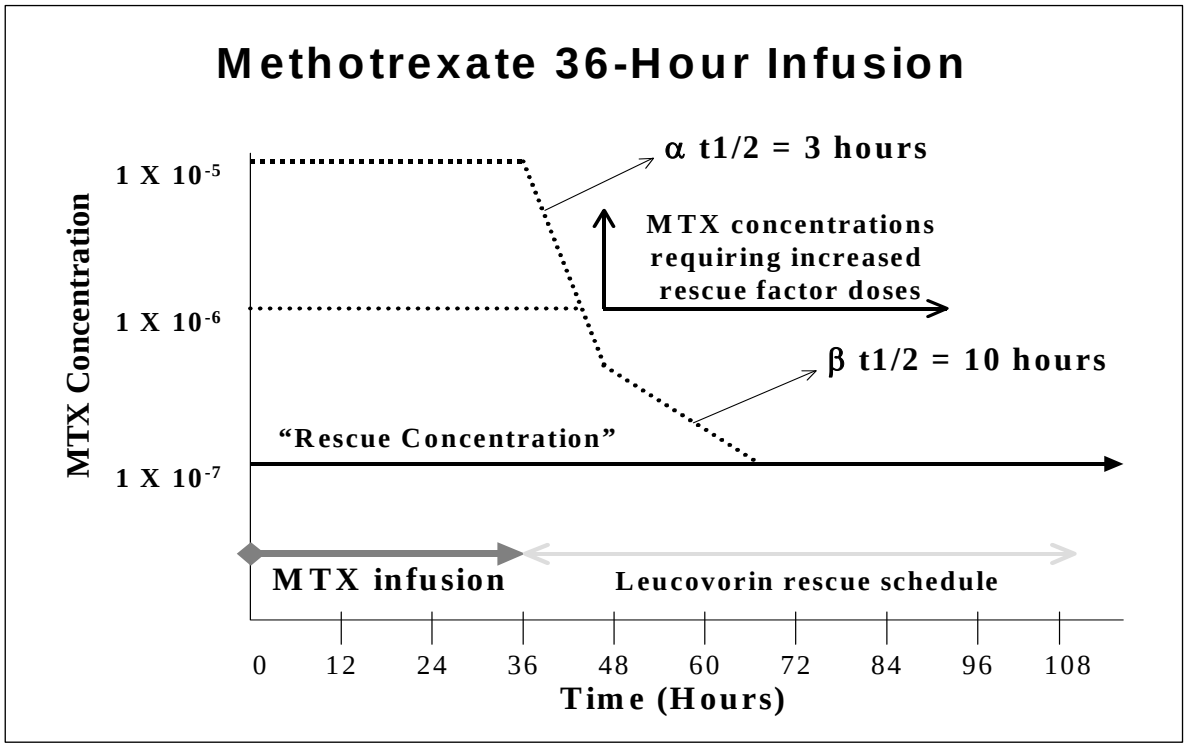
Metabolism

- Metabolism is minimal; 3 metabolic pathways
  - Intracellular polyglutamylation
    - Important pathway for selective retention of folates
    - Addition of up to 5 additional glutamate residues by the enzyme folyl polyglutamate synthetase (FPGS)
    - ACTIVE metabolite, contributes to cytotoxicity
    - Polyglutamylated MTX is potent DHFR inhibitor as MTX

- Hydroxylation
  - 7-hydroxy metabolite (low H_2O solubility) can accumulate leading to nephrotoxicity
  - 1/100th the affinity for DHFR (inactive)
- Removal of glutamate residue (DAMPA)
  - Conversion performed by intestinal bacteria
  - Low levels in plasma may interact with MTX assay but NOT clinical significant

Excretion

- Excreted unchanged in the urine with minor biliary secretion
- Bi or tri-exponentional elimination (see figure below)
  - α t½ ~ 3 hrs
  - β t½ ~ 10 hrs - **not apparent until concentrations < $5X10^{-7}$ molar**
- Primarily renal eliminated
  - Combination of GFR & TS
- At low concentrations correlates with GFR
  - **MTX $Cl_{(ml/min)}$ ~ 1.6 X $Clcr_{(ml/min)}$**
  - Normal MTX Cl = 40-400ml/min
- High concentrations saturation of TS which ↓ net renal Cl
  - **RENAL FUNCTION MOST IMPORTANT DETERMINANT OF MTX PHARMACOKINETICS**
- Hydration status and urine pH
  - More acidic pH = decreased Cl
- Drug interactions:
  - Reduce renal blood flow (e.g. NSAIDs)
  - Inhibit renal transport of MTX (e.g. sulfisoxazole, weak acids)
  - Nephrotoxic (e.g. cisplatin)



Adapted from Winters ME. *Basic Clinical Pharmacokinetics*, 3rd Edition.

MTX is usually administered in mg or gm doses

- Low dose 15-20mg/m^2 twice weekly up to high dose 1-12 g/m^2 every 1-3 weeks
- Plasma concentrations are reported in units of mg/L, μg/mL, and molar or micromolar units (usual range 10^{-8} to 10^{-6}). MW = 454gm/mole
- 1 micromolar would be equivalent to the following:
  - 1μM (micromolar)
  - 0.01 X 10^{-4} molar
  - 0.1 X 10^{-5}molar
  - 1.0 X 10^{-6} molar
  - 10 X 10^{-7} molar
  - 0.454 mg/L

Therapeutic/toxic plasma concentrations

- Normal therapeutic range – variable
- Toxic plasma range (increased risk)
  >10 X 10^{-6} molar (10 μM) at 24 hrs
  >1 X 10^{-6} molar (1μM) at 48 hrs
  >0.1 X 10^{-6} (0.1μM) or 1 X 10^{-7} at 72 hrs
- **NOTE: This is time after beginning of MTX infusion**

Toxicities

- Cytotoxic effects due to inhibition of DHFR
  – Function of both concentration & duration of exposure
- Pancytopenia (sometimes irreversible)
- Severe mucositis
- GI and skin desquamation
- Renal and hepatic dysfunction

Leucovorin rescue

- To ensure that MTX toxicities do not occur, rescue factor (citrovorin factor or leucovorin) is administered every 4-6 hours in doses that range from 10 to 500 mg/m^2.
- Usual course is 12 to 72 hours until the plasma concentration of MTX falls below the critical value of 1 X 10^{-7} molar.
- If MTX conc. > 1X10^{-6} molar at 48 hours, leucovorin rescue dose is usually increased to 50 to 100mg/m^2 every 3-6 hours until concentration < 1 X 10^{-7} molar; also see alternative dosing below:

MTX serum concentration ≥42 hr from ***beginning*** of infusion	Approximate leucovorin dose required
20-50 μmol	500 mg/m^2 IV q6hr
10-20 μmol	200 mg/m^2 IV q6hr
5-10 μmol	100 mg/m^2 IV q6hr
1-5 μmol	30 mg/m^2 IV or PO q6hr
0.6-1 μmol	15 mg/m^2 PO q6hr
0.1-0.5 μmol	15 mg/m^2 PO q12hrs
0.05-0.1 μmol	5-10 mg/m^2 PO q 12hrs

Adapted from Crom WR, Evans WE. Methotrexate. In: Evans WE, et al., eds. *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*, 3rd ed.

PENTOBARBITAL

1. Time of Sampling (*$63*)

   a. Relative to Dose

      2-3h after load
      12 and 24h after maintenance infusion begins

2. Recommended Frequency of Sampling

   Since dose is based on pharmacologic response, concentrations are usually not warranted to assess efficacy or toxicity.

3. Therapeutic Range*

   20-40 mcg/ml (therapeutic coma)

   **Variable. Titration to individual patient response (based on neurologic and hemodynamic factors) is required. Therapeutic benefits at levels > 50 mg/ml are yet unproven. Levels > 50 mg/ml should be dosed based on response.*

4. General Guidelines for Monitoring

   Initial Dose

   Load

   High dose regimen:

   25-30 mg/kg (infuse over 3h); C_{pk} = 25-30 mcg/ml (may see hypotension)

   Low dose regimen:

   5-10 mg/kg (infuse over 1-2h); C_{pk} = 5-10 mcg/ml

   Maintenance infusion

   1-3 mg/kg/h

Dosage Adjustments

Mini-boosts of 1 mg/kg may be given for every 1 mcg/ml desired increase in serum concentration.

Titrate maintenance infusion rate according to clinical response.

The following conditions must be met prior to pharmacist involvement in pentobarbital monitoring:

a. Patient must be on a ventilator.

b. An ICP monitor must be in place with an initial pressure reading recorded.

c. A Swan-Ganz catheter (or at minimum, a CVP line and arterial line) must be in place along with an initial hemodynamic profile recorded.

d. A urinary catheter must be in place.

5. Factors Altering Pentobarbital Disposition

Renal failure and dialysis - no specific dosage adjustment appears necessary.

Reidenberg (1976) Clin Pharmacol Ther. 20:67.
Wermeling (1985) Ther Drug Monit. 7:485.

No specific guidelines or recommendations are available for other patient subpopulations.

Pentobarbital induces the metabolism of other oxidatively metabolized drugs (e.g., phenytoin, theophylline). Enzyme inhibitors (e.g. cimetidine) may decrease pentobarbital Cl_s.

6. Pediatric Considerations

Same as adults

7. Other Suggested References

Woster (1990) Clin Pharm 9:762.
Wermeling (1987) Drug Intell Clin Pharm 21:459.
Heinemeyer (1986) Ther Drug Monit 8:145.
Bayliff (1985) Clin Pharmacol Ther 38:457.
Quandt (1984) Drug Intell Clin Pharm 18:105.
Schaible (1982) Pediatrics 100:655.

PHENOBARBITAL

1. Time of Sampling (*$63; saliva = $47*)

   a. Relative to Dose

   - trough within 1h prior to dose; any consistent time within dosing interval is acceptable due to long t½ ~ 5 days.
   - at ss ~ 3 – 5 weeks

2. Recommended Frequency of Sampling

   a. Routine Use in Stable Patients

   - initial level

   b. Use in Unstable Patients*

   - initial level
   - repeat level, as dictated by changes in concurrent disease state/drug therapy or the lack of adequate response to previously adequate doses, or signs/symptoms of toxicity. Patients in status epilepticus require more intensive monitoring.

   Note: Since at least 15 to 20 days are required to achieve steady state, a loading dose is usually given to rapidly place the patient in the therapeutic range. Levels obtained prior to steady state may be useful in verifying if actual level is close to predicted level (e.g. if 20 mcg/ml is the predicted steady state value, it will take one t 1/2 to reach a level of 10 mcg/ml).

3. Therapeutic Range

   10 – 40 µg/ml

   5 – 15 µg/ml (saliva)

4. General Guidelines for Monitoring

   a. Initial Dosing

   Load: $X_o^* = \frac{C \cdot V}{S \cdot F}$

   V = 0.7 L/Kg (adults)
   S = 0.9 (sodium salt)
   F = 1.0

   or

   20 mg/kg

   Infusion rate should not exceed 65 mg/min. Respiratory status should be closely monitored.

b. Maintenance Dose:

Usual adult dose: 1-3mg/kg/day in divided doses

$$X_o = \frac{\bar{c} \cdot Cl_s \cdot \tau}{S \cdot F}$$

S = 0.9 (sodium salt)
F = 1.0
Cl_s = 0.096 L/Kg/D (adults with normal hepatic function)

It is common practice to give 25% of the total maintenance dose for one week, ↑ to 50% the second week, ↑ to 75% the third week, and ↑ to the full dose the fourth week to minimize toxicity.

$\bar{c}$ (at ss) produced by any given maintenance dose is approximately 10 times the daily dose in mg/kg (e.g. 2 mg/kg - 20 mcg/ml).

For patients with liver disease, empirically decrease maintenance dose of phenobarbital by 30%.

c. Dosing Adjustments

$$Cl_s = \frac{S \cdot F \cdot X_o}{\bar{c} \cdot \tau}$$

Calculate actual Cl_s, based on $\bar{C}$ (level, usually obtained at trough), τ, S,F, and X_o (dose administered).

$$X_o = \frac{\bar{c} \cdot Cl_s \cdot \tau}{S \cdot F}$$

Calculate new maintenance dose.

5. Factors Influencing Phenobarbital Disposition

Liver disease: See 4a. [Alvin (1975) J Pharmacol Exp Ther 192:224].

Pharmacokinetic interactions: PB induces metabolism of other oxidatively metabolized drugs (e.g. carbamazepine, phenytoin, warfarin, steroids, theophylline) but PB itself does not require dosage adjustment. Exceptions include: valproic Acid and chloramphenicol which inhibit PB metabolism and require an empiric PB dosage adjustment downward by 50%.

Pregnancy: ↑ PB Cl_s

6. Pediatric Guidelines:

Neonates

LD: 20-30 mg/kg; V = 0.9-1.1 L/Kg
MD: < 32 wks (postconceptional age) 1-2 mg/kg/D
≥ 32 wks (postconceptional age) 3-5 mg/kg/D

Infants and Children

LD: 20-30 mg/kg; V = 1.0 L/Kg (V in older children approaches that of adults)
MD: 5-10 mg/kg/D (Start MD 12 hours after LD)

- Infants 5-6 mg/kg/d in 1-2 divided doses
- 1-5 years: 6-8 mg/kg/day in 1-2 divided doses
- 5-12 years: 4-6 mg/kg/day in 1-2 divided doses
- 12 years: 2-3 mg/kg/day in 1-2 divided doses

Other Considerations

Infusion rate should not exceed 2-3 mg/kg/min. Normal loading doses should be administered over 10 min. Respiratory depression is more commonly seen in patients who have recently received chloral hydrate or parenteral benzodiazepines prior to initiation of phenobarbital therapy.

Tablet and elixir dosage forms are interchangeable.

Dosage forms available:

Elixir:	4mg/ml, 30mg/7.5ml, 20mg/5ml, 15mg/3.75ml
Injection:	10mg/ml
Tablets:	15mg, 30mg, 60mg, 100mg

PHENYTOIN

1. Time of Sampling (*$53 for C_{total}; $69 for C_{free}; $47 for saliva)*

   a. Relative to Dose

   - Trough within 1 hr prior to dose
   - At steady state *(The time to achieve steady state is variable, ranging from 3 to 50 days, due to saturation kinetics).*
     - After **oral administration** of **Kapseals**: **average half-life ~ 22 hrs** (Prod Info Kapseals® Dilantin®, 2000) but can range from 7 to 42 hrs; value is variable due to the saturation kinetics
     - After **intravenous administration**, half-life ranges from 10 to 15 hrs (Prod Info Phenytoin Sodium Injection, USP, 2000).

2. Recommended Frequency of Sampling

   a. Routine Use in Stable Patients

   - One steady-state concentration
   - Repeat concentration at steady-state after each dosage adjustment

   b. Use in Unstable Patients

   - After a loading dose, an initial level may be drawn to assess attainment of therapeutic concentrations. (Recommended to be drawn ~2 hours after IV LD and 6-8 h after oral LD).
   - Trough in 3 to 4 days
   - Weekly thereafter
   - The frequency of sampling is also dictated by:
     - Changes in concurrent disease states or drug therapy
     - Lack of adequate response to previously adequate doses
     - Signs/symptoms of toxicity
   - Patients with recurrent status epilepticus require more intensive monitoring.

3. Therapeutic Range

   Total: 10-20 µg/mL (assuming normal albumin)

   Free: 1-2 µg/mL (normal; at body temperature)
   0.8 – 1.6 µg/mL* (therapeutic range reported by UKCMC Clinical Lab)
   **** The reported free concentration at UKCMC is adjusted since the assay is performed at room temperature which alters protein binding.***

   Saliva: 1-2 µg/mL

4. General Guidelines for Monitoring

a. Loading Dose

Use **TBW** unless patient is obese (>125% IBW).
If obese: adjusted weight = IBW + (1.33)(TBW-IBW).

NOTE: Phenytoin is lipophilic and has a larger Vd in obese patients. The above equation calculates a phenytoin dosing weight greater than ABW. Use the equation to calculate the dose, and then administer a dose that is comfortable based on experience and condition of the patient. Sometimes the calculated dose may need to be reduced initially (i.e. ½ the dose). Administer the dose, and then reassess the patient based on clinical response or serum concentrations for subsequent doses.

$$X_o^* = \frac{C \cdot V}{S \cdot F}$$

V = 0.7 L/kg
S = 0.92 (sodium salt; caps, inject)
1.0 (acid; chewtabs, suspension)
F = 1.0 (oral - only if given in divided doses); variable with suspension

OR

X_o^* = 14-16 mg/kg
(Stable patients/seizure prevention)

= 16-20 mg/kg
(control of status epilepticus)

- May be administered as one dose, or in 3 divided doses given q 4 h (IV or PO); **Suggested max single oral dose = 400mg due to erratic and delayed absorption.**
- Avoid IM injections - painful; erratic absorption
- IV infusion rate is usually 10-25 mg/min, although some patients may tolerate up to 50 mg/min (**MAXIMUM RECOMMENDED RATE**). Blood pressure should be checked q 5 min x 3, then q 15 min until 1 hr after the end of the infusion.
- When administered by a floor nurse, the rate should not exceed 10 mg/min. Blood pressure should be checked q 15 - 20 min. Hypotension may occur due to propylene glycol (diluent).

b. Maintenance Dose

1. Initial

- Empirically based on body weight: **5-7 mg/kg/day**

  For obese patients, the maintenance dose should be based on IBW.

- Alternative: Ludden Method and estimate both K_m and V_m from Appendix 1.

$$\text{Dose} = \frac{(V_m)\cdot(C_{ss})\cdot(\tau)}{(K_m + C_{ss})\cdot(S)\cdot(F)}$$

F = 1.0
S = 0.92

If hypoalbuminemia, use the ADJUSTED CONCENTRATION (see 6A)

2. Dosage Adjustment using Ludden Method [Ludden (1976). Lancet 1:307].

Assumptions:
1. Steady state
2. Patient compliance
3. Normal renal and hepatic function
4. Normal albumin

a) On basis of a **single concentration** at **steady state** with the same dose:

$$(S)\cdot(F)\cdot\frac{\text{Dose}}{\tau} = \frac{(V_m)\cdot(C_{ss})}{(K_m + C_{ss})}$$

C_{ss} = measured concentration
Dose = present dose

Usually assume K_m (less variable) and rearrange the above equation to estimate V_m using the single steady-state concentration:

$$V_m = \frac{(S)\cdot(F)\cdot(\frac{\text{Dose}}{\tau})\cdot(K_m + C_{ss})}{(C_{ss})}$$

Then calculate a new dosage using the equation below by using the assumed K_m, the calculated V_m and the desired concentration and Tau.

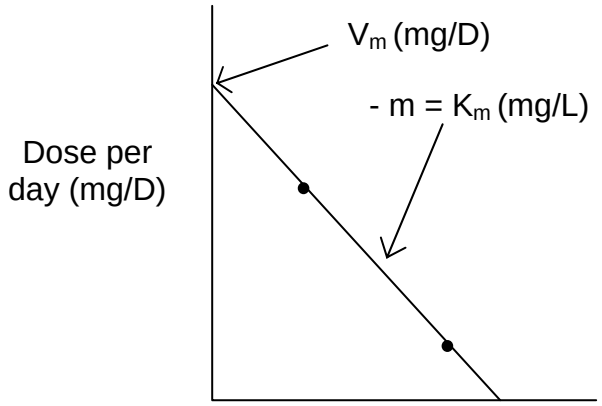
$$\text{Dose} = \frac{(V_m)\cdot(C_{ss})\cdot(\tau)}{(K_m + C_{ss})\cdot(S)\cdot(F)}$$

C_{ss} = desired concentration
Dose = new dose

Recalculate C_{ss} after rounding dose:

$$C_{ss} = \frac{\left(\frac{\text{Dose}}{\tau}\right)(S)(F)(K_m)}{(V_{max}) - \left[\left(\frac{\text{Dose}}{\tau}\right)(S)(F)\right]}$$

b) On basis of **<u>two concentrations</u>** at steady state obtained at **<u>different</u>** daily doses.



$$Km = -\frac{rise}{run}$$

or

$$Vm = \text{Dose per day} + (Km * \frac{\text{Dose per day}}{Css})$$

$$b = y - mx$$

After calculating individual patient's K_m and V_m as shown above, may calculate new dose.

$$\text{Dose} = \frac{(V_m)\cdot(C_{ss})\cdot(\tau)}{(K_m + C_{ss})\cdot(S)\cdot(F)}$$

C_{ss} = desired level
Dose = new dose

3. <u>Mini-loading</u>

Used when patient has sub-therapeutic concentration, to immediately put patient in the therapeutic range before starting new maintenance dose.

$$\text{Mini-loading dose} = \frac{(V_d)\ (C_{ss}\ \text{desired} - C_{ss}\ \text{measured})}{S\cdot F}$$

4. <u>Toxic levels</u>

Used when concentration is too high, to determine how long (t) until patient achieves concentration in therapeutic range (C); C_o = measured concentration.

$$t_{(days)} = \frac{[K_m\ x\ (\ln\ \frac{C_o}{C})] + (C_o - C)}{\frac{V_{max}}{V_d}}$$

(integrated form of Michaelis-Menten equation)

5. Pediatric Guidelines

- Vd – 1-1.2 L/kg (neonates)
  0.8-0.9 L/kg (term)
  0.7 L/Kg (infants/children)

- Km = 3-9mg/L; Vm = 5-20mg/kg (infants/children)

- Loading dose: same loading dosing equation as adults

- Maintenance dose: 8-10 mg/kg/day (oral); 5-8 mg/kg/day (iv)

  - Maintenance dose should be administered in 2-3 divided doses (some pediatric patients may require q8hr dosing due to increased clearance; once-daily dosing is usually not possible

- Infusion rate: 12.5 mg/m^2/min maximum
  3-5 mg/kg/min (avg. 10-12 mg/min)

- **REMEMBER TO SHAKE THE PHENYTOIN SUSPENSION BOTTLE WELL TO PROVIDE CONSISTENT DOSE!**

- Stagger dosing (at least one hour) with feedings - if on formula (decreases absorption - similar to enteral feeding products)

- Avoid phenytoin in neonates with indirect hyperbilirubinemia requiring phototherapy

6. Other Factors That May Influence Phenytoin Disposition

a) Hypoalbuminemia (normal albumin = 3.2 – 4.6 g/dL):

↓ Protein binding sites
↑ Free fraction (ff)
↓ Total concentration (will not be reflective of free concentration of 1-2 mcg/ml since free fraction is increased)

The total phenytoin concentration* can be adjusted to account for the decrease in albumin using the following equation:

$$C_{predicted} = \frac{C_{observed}}{(0.25 \times alb) + 0.1}$$

$C_{predicted}$ = C_{total} adjusted for ↓ albumin
$C_{observed}$ = observed phenytoin concentration

**Based on protein binding when determined at room temperature (25º C).*

Anderson GD, Pak C, Doane KW et al. Revised Winter-Tozer equation for normalized phenytoin concentrations in trauma and elderly patients with hypoalbuminemia. *Ann Pharmacother.* 1997 Mar;31(3):279-84.

The free fraction can also be adjusted using the following equation:

$$fub = \frac{1}{1 + (2.1 \times alb)}$$

Winter MG, Tozer TN. Phenytoin. In: Evans WE, Schentag JJ, Jusko WJ, eds. Applied Pharmacokinetics. Principles of therapeutic drug monitoring. 2nd ed. Spokane: Applied Therapeutics Inc.;1986.

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b) Uremia - displacement from protein binding sites

↑ free fraction
↓ total concentration needed to achieve free phenytoin concentration of 1-2 mcg/ml

↑ Vd (Adjust Vd for low albumin): V_d (L/kg) = $\frac{6.5}{1 + alb}$

Winter and Tozer in Applied Pharmacokinetics. 2nd Ed. p. 501.
Boobis (1977) Clin Pharmacol Ther. 22:147.
Hooper (1974) Clin Pharmacol Ther. 15:276.

c) Obesity

↑ Vd (Use 0.7 L/kg)
↔ Free fraction unchanged
↔ Clearance unchanged

Abernathy (1985) Arch Neurol. 42:468.

d) Elderly

↓ V_m (about 21% less phenytoin per day is required to maintain C_{ss} of 15 mcg/ml)
↑ free fraction
↓ total concentration needed to achieve free phenytoin concentration of 1-2 mcg/ml

Bauer (1982) Clin Pharmacol Ther. 31:301.

e) Critically ill

↔ Vd unchanged
↔ K_m and V_m unchanged
↑ free fraction may increase with time (even when albumin is unchanged)
↓ total and free conc. may decrease with time, warranting higher maintenance doses.

Boucher (1987) Clin Pharm. 6:881.

f) Drug interactions - several types (phenytoin substrate for CYP 2C9/2C19).

- Displacement from protein binding sites results in ↓ total conc. needed to achieve free conc. of 1-2 mcg/ml. ex. -valproic acid, phenylbutazone, aspirin and sulfa drugs.
- Enzyme Inducers - increase phenytoin Cl ex. -phenobarbital, carbamazepine and folic acid
- Enzyme Inhibitors - decrease phenytoin Cl ex. -cimetidine, chloramphenicol, valproic acid, disulfiram and isoniazid
- Phenytoin is also a potent enzyme inducer and increases Cl of many drugs including theophylline, oral anticoagulants and steroids.
- **HOLD TUBE FEEDS 1 HR BEFORE AND 1 HR AFTER PHENYTOIN SUSPENSION DOSE PER FEEDING TUBE. ADJUST TUBE FEED RATE ACCORDINGLY.**

7. Other Selected References

- oral loading - Jung (1980) Clin Pharmacol Ther. 28:479.
- utility of Ludden method - Ludden (1976) Clin Pharmacol Ther. 21:287.

8. Population Parameters Appendix I.

APPENDIX 1
PHENYTOIN PHARMACOKINETICS

AGE (years)	*PARAMETERS* Vmax (mg/kg/day)	Km (mg/L)	Vd (L/kg)
Adult			
20-39	7.5	5.7	0.7
40-59	6.6	5.4	0.7
60-79	6.0	5.8	0.7
Pediatric			
0.5-3	14.0	6.6	1.6
4-6	10.9	6.8	
7-9	10.1	6.5	
10-16	8.3	5.7	0.6

Dosage forms available:

Capsule 30mg, 100mg
Chewtab 50mg
Suspension 125mg/5ml (5mg/ml)
Injection 100mg/2ml (50mg/ml)

FOSPHENYTOIN

Introduction

- Water soluble prodrug intended for parenteral administration
- Active metabolite is phenytoin
- **Dose should be expressed, labeled, and ordered in phenytoin equivalents (PE).** ***1.5mg fosphenytoin = 1mg phenytoin sodium but on vial FOSPHENYTOIN is written as PE/ml, not mg/ml*****.**
- Fosphenytoin is very **EXPENSIVE** compared to injectable sodium phenytoin (i.e., 1 gram fosphenytoin ~ $90 vs. 1 gram phenytoin ~ $3)

- Potential advantages:
    1. Less phlebitis & local tissue damage at injection site (fewer return visits, lower tx costs, & fewer lawsuits)
    2. Less risk of hypotension with rapid IV loading
    3. Less frequent need to restart IV lines due to local irritation
    4. Elimination of need of filter in IV line
    5. IM administration possible
    6. Greater patient satisfaction due to less morbidity

Absorption/Bioavailability

- IV: max concentrations achieved after at the end of infusion but
- IM: peak concs ~ 30min post dose

Distribution

- 95 – 99% protein bound, primarily albumin
- increases with dose/rate, ranges from 4.3 to 10.8L

Metabolism/Elimination

- phenytoin cleaved from the prodrug by phosphatase enzymes
- conversion t½ ~ 8-15 minutes
- complete conversion IV ~ 2hrs; IM ~ 4hrs
- NO drugs are known to interfere with the conversion

Dosing Guidelines & Monitoring

- Dosage similar to phenytoin BUT use PHENYTOIN EQUIVALENTS
- Because of risk of hypotension, **NOT recommended to exceed 150 PE/min**
- Need to wait ***at least 2 hours after IV dose and 4 hours after IM dose*** for complete conversion to measure serum concentrations

Suggested patient criteria for administration of fosphenytoin*:

1. Age: <7yo or >60yo
2. History of underlying cardiovascular problems or preexisting hypotension)
3. Chronic or acute debilitating illness, emaciation, hyponatremia, peripheral vascular disease, hemodynamic instability, or sepsis
4. Poor intravenous access qualified by one of the following: size smaller than the antecubital fossa vein, catheter size < 20 gauge, no preexisting central venous catheter
5. Pain intolerance with phenytoin sodium recognized.

***Guidelines for Fosphenytion Use (Meek PD, et al. *Arch Intern Med*. 1999; 159:2639-2644)**

FREE PHENYTOIN

Policy:

1. Any medical (or surgical or other) service can order free phenytoin levels if patients meet criteria (See Appendix II).

2. Physicians on the Neurology service can request or interpret their own results, although the Clinical Pharmacokinetics Service will provide clinical interpretation if consulted.

3. For services other than Neurology, the following will apply:

   - Once the TDM Lab receives a request for a free phenytoin level, TDM Lab will notify the pharmacist on that service or contact the Clinical Pharmacokinetics Service (for uncovered services). The pharmacist will monitor the criteria and provide essential clinical input regarding the need for the level.

   - The pharmacist should make sure that a total concentration is ordered concomitantly with the free concentration to assess free fraction.

   - The pharmacist will notify TDM Lab if the assay should be run or cancelled. If an order is to be cancelled, the pharmacist needs to notify the physician first and document (in the patient's chart) the recommendation to cancel the level.

   - Once the TDM Lab runs the assay, the result will be reported in the computer. The pharmacist will write a note in the patient's chart and provide an interpretation and/or recommendation.

   - A pharmacist will be available from 08:00 to 17:00 Monday-Friday to provide clinical interpretation. Any request received outside of this time frame will be reviewed prior to the TDM Lab cut-off time the next day.

4. The therapeutic range of free phenytoin concentrations will be reported as 0.8 to 1.6 mcg/ml.*

5. The patient charge for the free phenytoin assay is $89 per sample.

* *Derived from TDM Lab assay (performed at 25^{o}C) data of 8% free fraction in patients with normal albumin [i.e. 8% of the usual total therapeutic range for total concentrations (10 to 20 mcg/ml) is 0.8 to 1.6 mcg/ml].*

Appendix II.

Free phenytoin concentrations should be reserved for the situations described below. For example, a "normal" patient with normal albumin and normal renal function who is not on concurrent medications that alter phenytoin protein binding or clearance would not warrant a free phenytoin concentration.

A free phenytoin concentration is warranted when:

1. The total phenytoin dosage is >7 mg/kg/day and the total concentration is <10 mcg/ml.

or

2. A patient is seizure-free at a total level of <10 mcg/ml and you need to determine whether a dosage increase is necessary.

or

3. A patient is exhibiting signs of toxicity at a dosage of ≤7 mg/kg/day and has a total concentration of ≤20 mcg/ml.

or

f. A patient is in a unique subpopulation (e.g. a pregnant female, a patient on multiple anticonvulsant therapy, etc.)

Modified Michaelis – Menten Equation for adjusting phenytoin dosage based on steady-state free concentration.

- Use a steady-state free concentration (C_{ss}^{free}) to calculate free fraction (fub) = $\frac{C_{free}^{ss}}{C_{total}^{ss}}$.

- Use C_{ss}^{free} , fub, K_o, and <u>population</u> K_m to calculate V_m (mg/day) with equation #4.

- Use the <u>desired</u> C_{ss}^{free} (UKCMC range: 0.8-1.6mg/L), fub, Vm, and Km to calculate for a new dosage, K_o (mg/day) with equation #3.

Derivation of the Modified Michaelis - Menten Equation:

1.) $$\frac{K_o}{fub} = \frac{V_m \cdot C_{ss}^{total}}{fub \cdot (K_m + C_{ss}^{total})} = \frac{V_m \cdot C_{ss}^{total}}{(fub \cdot K_m) + (fub \cdot C_{ss}^{total})}$$

Multiply both sides by fub :

2.) $$K_o = \frac{V_m \cdot (C_{ss}^{total} \cdot fub)}{fub \cdot (K_m + C_{ss}^{total})}$$

Substitute C_{ss}^{free} *for* $(C_{ss}^{total} \times fub)$:

3.) $$\therefore K_o = \frac{V_m \cdot C_{ss}^{free}}{(fub \cdot K_m) + C_{ss}^{free}}$$

Equation rearranged to solve for V_m :

4.) $$V_m = \frac{K_o \cdot [(fub \cdot K_m) + C_{ss}^{free}]}{C_{ss}^{free}}$$

Rhoney DH, Leader WG, Chandler MHH. Modified Michaelis-Menten Equation for Estimating Unbound-Phenytoin Concentrations. *Clin Pharm.* 1993:12:913-917.

PROCAINAMIDE

1. Time of Sampling (*$32, PA and NAPA*)

   a. Relative To Dose

      - trough within 30 min prior to dose
      - at ss (12 to 25 hours after initiation of therapy, in patients w/ normal renal function).

2. Recommended Frequency of Sampling

   a. Routine Use in Stable Patients

      - initial level (at ss)

   b. Use in Unstable Patients

      - After a loading dose, an initial level may be drawn to assess attainment of therapeutic concentrations.
      - Repeat level every 2 to 3 days [or as dictated by: changes in concurrent disease states or drug therapy; lack of adequate response to previously adequate doses (e.g. after recurrence of arrhythmia to determine if subtherapeutic or unresponsive to therapeutic concentrations); and/or signs/symptoms of toxicity].

3. Therapeutic Range

   4-10 mcg/ml (procainamide)*

   5-30 mcg/ml (NAPA); NAPA > 20 potentially toxic**

   * *PA commonly used at EPS; level documented here (if drug effective) should be the target conc. chronically.*

   ** *TDM Lab automatically reports NAPA levels in conjunction w/ procainamide levels.*

4. General Guidelines for Monitoring

a. IV Dosing

Initial Dosing:

- 17 mg/kg (if obese, use IBW) loading infusion (over 1h), followed immediately by a 2.8 mg/kg/h (ABW) maintenance infusion

  Patients w/ moderate impairment of renal function or cardiac output: ↓ maintenance infusion rate by 1/3.

  Patients w/ severe impairment of renal function or cardiac output: ↓ maintenance infusion rate by 2/3; ↓ loading infusion to 12 mg/kg.

Dosage Adjustments

$$C_{ss} = \frac{F \cdot S \cdot K_o}{Cl_s}$$

- If rapid achievement of the new C_{ss} is desired, additional loading doses of 2 mg/kg (IBW) may be administered for each 1 mcg/ml increase in plasma concentration desired.

- Avoid aggressive dosage changes (e.g. doubling dosing rate) secondary to potential disproportionate increases in plasma concs.

Alternative Dosing Approach

- Administer 100 mg (infuse over 2 min) q 5 min until control of arrhythmia or attainment of a 1 gm cumulative dose, or development of toxicity (e.g. QRS > 50% baseline, hypotension).

- Follow with maintenance infusion of 2 to 6 mg/min.

b. Oral Dosing*

For patients previously on IV infusion:

$$X_o = \frac{\bar{C}_{po} \cdot (\frac{K_o}{\bar{C}_{iv}}) \cdot \tau}{F}$$

X_o = oral dose
$C_{(po)}$ = desired conc. (w/ po dosing)
$C_{(iv)}$ = measured conc. (w/ IV dosing)
K_o = infusion rate (mg/h)
F = 0.83, variable
S = 0.87 (HCl salt)

S-R preps: τ = 6h
Immediate-release preps: τ = 3-4h

Capsules: 250mg, 375mg, 500mg
SR tablets: 250mg, 500mg, 750mg

ER: 1gm (Procainabid®)

Changing from IV to oral prep:

S-R: Administer oral prep; d/c IV 2 h later
Immediate-release: Administer oral prep; d/c IV 1 h later

For patients not previously on IV infusion

- Empiric: 10-15 mg/kg (IBW) load
  35-50 mg/kg (ABW)/day maintenance

  Oral therapy should be initiated with immediate-release preps.

- Estimation of Cl_s:

  $Cl_{s\ (ml/min/70kg)} = [Cl_m + (Cl_r \times \text{fraction of renal fx remaining})]$

  $Cl_{s\ (ml/min/70kg)} = [275_{(ml/min)} + (275_{(ml/min)} \times (Cl_{cr} / 100))]$

- Dosage Adjustments:

  S-R preps: $\bar{c} = \frac{S \cdot F \cdot X_o}{Cl_s \cdot \tau}$ V = 2L/kg

  Immediate-release preps: $C_{tr}^{ss} = \frac{S \cdot F \cdot X_o}{V} * e^{-K\tau} * (\frac{1}{1 - e^{-K\tau}})$

  - Patients w/ moderate impairment of renal function or cardiac output: ↓ maintenance dose by 1/3.
  - Patients w/ severe impairment of renal function or cardiac output: ↓ maintenance dose by 2/3.

5. NAPA (N-acetylprocainamide)

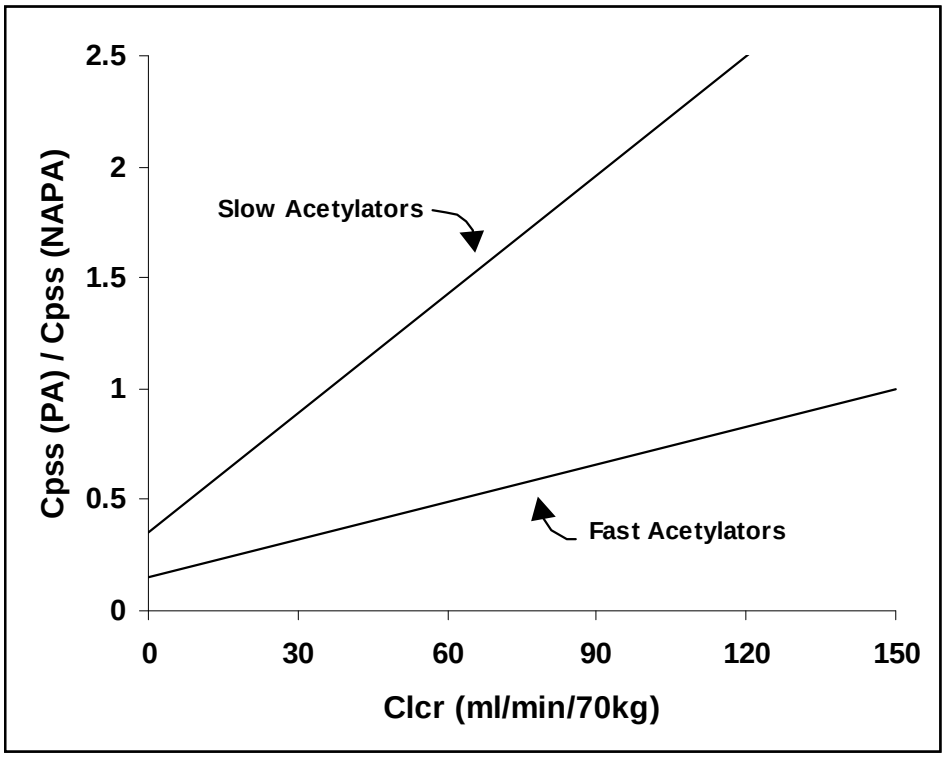
- Recommended for measuring as an index of toxicity, in patients w/ moderate to severe renal impairment.

- Risk of toxicity should be assessed based on individual concentrations of PA and NAPA concentrations.

- Acetylator phenotype:

  - Caucasians, African-Americans, Indians, Mexicans - 50 to 65% are slow acetylators.
  - Eskimos, Chinese, Japanese - 80 to 90% are rapid acetylators.
  - Slow acetylators excrete a smaller fraction of a PA dose as NAPA, possibly resulting in unexpectedly high plasma concs. of PA and predisposition to toxicity (if pt has renal dysfunction).

Plot used to determine if patient is slow or fast acetylator using average Cp_{ss} (PA):Cp_{ss}(NAPA) ratio and Clcr (ml/min/70kg). Ratios of procainamide to NAPA concentrations, which lie between the lines for fast and slow acetylators, would be assigned to the closest adjacent line. Phenotype status is uncertain for patients with Cp_{ss} (PA):Cp_{ss}(NAPA) ratios that are intermediate.



Adapted from Basic Clinical Pharmacokinetics, M.E. Winter, ed., 1994.

6. Drug Interactions

- Cimetidine: empirically ↓ PA dose by 40%
- Amiodarone: empirically ↓ PA dose by 20%
- Trimethoprim: ↓ Cl_s

7. Suggested References

Applied Pharmacokinetics (1986), 2nd ed., p. 682-711.

Dosing:	Lima (1978) Eur J Clin Pharmacol 13:303.
	Giardina (1973) Ann Intern Med 78:183.
Obesity:	Christoff (1983) Drug Intell Clin Pharm 17:516.
Elderly:	Reidenberg (1980) Clin Pharmacol Ther 28:732.
Renal Impairment:	Gibson (1977) Kidney Int 12:422.
Hepatic Impairment:	DuSouich (1977) Clin Pharmacol Ther 22:588.
Cardiac Impairment:	Lima (1979) Am J Cardiol 43:98.
Drug Interactions:	Christian (1984) Clin Pharmacol Ther 36:221.
	Saal (1984) Am J Cardiol 53:1264.

QUINIDINE

1. Time of Sampling***** (*$27*)

   a. Relative to Dose

   - trough within 1 h prior to dose
   - at ss (4 to 5 estimated half-lives); t½ ~ 7hrs, get Css in 2-3 days

   ****NOTE: Samples are sent to an outside laboratory with results reported in 2-3 days)***

2. Recommended Frequency of Sampling

   a. Routine Use in Stable Patients

   - initial level (at ss)

   b. Use in Unstable Patients

   - After a loading dose, an initial level may be drawn to assess attainment of therapeutic concentrations.

   - Repeat level every 2 to 3 days or as dictated by changes in concurrent disease states or drug therapy; lack of adequate response to previously adequate doses (e.g. after recurrence of arrhythmia to determine if subtherapeutic or unresponsive to therapeutic concentrations); and/or signs/symptoms of toxicity.

3. Therapeutic Range

   - 2-5 mcg/ml

4. General Guidelines for Monitoring

   a. Initial Dosing*

   Load (PO): $X^{*}_{o} = \frac{C \cdot V}{S \cdot F}$

   V = 2.7-3 L/kg (normals)
   1.8 L/kg (CHF)
   3.8 L/kg (cirrhosis)

   sulfate: S = 0.83; F = 0.73 (PO)
   gluconate: S = 0.62; F =0.70 (PO), 1.0 (IV), variable (IM)
   polygalacturonate: S = 0.60; F= 0.70 (PO)

   (IV): 6-10 mg/kg

- Oral loads should be divided (maximum 400 mg per single dose, e.g. 400 mg q 3h x 3 doses) to minimize GI upset.

- 25% dosage reduction needed for patients with CHF. Infusion rate should not exceed 25 mg/min to minimize hypotension.

Maintenance Dose*

- Usual daily dose (PO):

  sulfate 23 mg/kg/D in divided doses (e.g. q6h; S-R, q 8-12h)

  gluconate 30 mg/kg/D in divided doses (e.g. q8h)

- Usual daily dose (intermittent IV infusion or IM**):

  gluconate 17-21 mg/kg/D in divided doses (e.g. q8h)

  * *Use IBW for morbidly obese patients.*
  ** *With IM may see transient ↓ in conc. following switch from po to IM, due to slow tissue release.*

b. Dosage Adjustment

Sustained release product:

$$Cl_s = \frac{S \cdot F \cdot X_o}{\bar{c} \cdot \tau}$$

Calculate actual Cl_s, based on $\bar{c}$ (level, usually obtained at trough), τ,S,F, and X_o (dose administered).

$$X_o = \frac{\bar{c} \cdot Cl_s \cdot \tau}{S \cdot F}$$

Calculate new maintenance dose

Rapidly absorbed oral product or intermittent IV infusion:

$$C_{tr}^{ss} = C_{pk}^{ss} * e^{-K\tau} = \frac{S * F * Xo}{Vd} * e^{-K\tau} * \frac{1}{1-e^{-K\tau}}$$

5. Alterations in Quinidine Disposition

a. Cl_s

normal	=	4.5 ml/min/kg, variable
CHF	=	3 - 3.9 ml/min/kg
cirrhosis	=	3.8 ml/min/kg
elderly	=	2.6 ml/min/kg
children (< 12 yo)	=	7.7 ml/min/kg

b. Protein Binding (NL = 60 - 90%)

↑ f — liver disease; cyanotic congenital heart disease; concomitant heparin therapy; neonates, infants <18 mo. old

↓ f — post-trauma; surgery; cardiac arrest; MI

↔ f — renal dysfunction; CHF; respiratory insufficiency hyperlipoproteinemia

Note: Quinidine is a low extraction drug: $C_{total} = \frac{K_o}{f \cdot Cl_I}$; $C_{free} = \frac{K_o}{Cl_I}$

c. t½:

normals	6-7h, variable
CHF; renal dysfunction	↔
cirrhosis	↑ (9h)
elderly	↑ (9.7h)
children (<12 yo)	↓ (2-3 h)

d. Drug Interactions

- Quinidine is a potent **inhibitor** of **CYP2D6** (TCA, β-blockers)
- Phenobarbital, phenytoin, and rifampin ↑ Cl_s of quinidine.
- Cimetidine and amiodarone ↓ Cl_s of quinidine; ↓ quinidine dose by ≅ 25% (w/ cimetidine) and ≅ 37% (w/ amiodarone)
- Nifedipine ↑ Cl_s of quinidine (poorly documented)
- Decreases digoxin Cl_s by 50%
- Antacids/antidiarrheals ↓ absorption

6. Miscellaneous

Formulary quinidine products, UKMC:

quinidine sulfate	tablet 200 mg capsule 300 mg
quinidine gluconate	S-R tablet (Quinaglute Dura-Tab®) 324 mg injection 80 mg/ml, 10 ml vial

7. Suggested References

Applied Pharmacokinetics (1992), 3rd ed., p. 23-1 – 23-22.

CHF:	Ueda (1978) Clin Pharmacol Ther 23:158.
Cirrhosis:	Kessler (1978) Am Heart J 96:627.
Renal dysfunction:	Levy (1976) Clin Res 24:85A
Elderly:	Ochs (1978) Am J Cardiol 42:481.
Pediatrics:	Szefler (1982) Pediatrics 70:370.
Drug interactions:	Hardy (1983) Am J Cardiol 52:172. Saal (1984) Am J Cardiol 53:1264.

THEOPHYLLINE

1. Time of Sampling *($60)*

   a. Relative to Dose

   - Oral (tablet, liquid, S-R preps with duration of absorption < τ, e.g. Slo-Phyllin Gyrocaps).

     - trough within 1h prior to dose

   - S-R preps or continuous infusion with duration of absorption $\geq \tau$
     e.g. Theodur

     S-R preps:
     - tr within 1h prior to dose; any consistent time within dosing interval is acceptable if S-R preparation.

     Continuous infusion:
     - Single level

       $\geq$ 24h after dosage adjustment made during continuous infusion (w/o bolus).

     - Multiple levels (for use with Chiou equation):

       Continuous infusion (w/o bolus): anytime during true zero-order infusion with 2 levels separated optimally by one t½.

       Continuous infusion (with bolus): $\geq$ 1 hour after bolus as 1st sampling time and one t½ later as 2nd sampling time.

   - Intermittent injection

     - trough within 1h prior to dose

   b. Relative to Steady State

   After at least 4-5 half-lives (normal t½ ~8-9hrs)

2. Recommended Frequency of Sampling

   a. Routine Use in Stable Patients

   - initial level

   b. Use in Unstable Patients*

   - initial level
   - repeat level every 2 to 3 days

   **The frequency of sampling is dictated by changes in concurrent disease state/drug therapy or the lack of adequate response to previously adequate doses, or signs/symptoms of toxicity. Patients in acute respiratory distress require more intensive monitoring*.

3. Therapeutic Range

   - 5-20 mcg/ml
   - 6-13 mcg/ml for apnea of prematurity

4. General Guidelines for Monitoring

   a. Initial Dosing

Aminophylline (Theophylline) Dosage Guidelines*
For patients not currently receiving theophylline products:

Age	Loading Dose **mg/kg (IBW)***	Maintenance Dose *For next 12 hours* **mg/kg/hr (IBW)***	Maintenance Dose *Beyond 12 hours* **mg/kg/hr (IBW)***
Infants (6 weeks – 6 months)	6 (5)	0.5 (0.4)	Dosage should be adjusted based on serum theophylline concentrations
Children (6 months – 1 year)	6 (5)	0.6-0.7 (0.48-0.56)	
Children (1 year – 9 years)	6 (5)	1-1.2 (0.8-1.0)	1.0 (0.8)
Children (9 – 12 years) & young adult smokers	6 (5)	0.9 (0.72)	0.8 (0.64)
Children (12-16 years)	6 (5)	0.7 (0.55)	0.8 (0.7)
Otherwise healthy nonsmoking adults	6 (5)	0.7 (0.55)	0.5 (0.4)

**Equivalent anhydrous theophylline dose in parenthesis*

Theophylline maintenance dosage guidelines for patients not currently receiving theophylline products. (Hendeles L, Jenkins J, Temple. Revised FDA labeling guideline for theophylline oral dosage forms. *Pharmacotherapy* 1995;15(4):409-427.)

Age	Initial Dosage[a]	Final Dosage[a]
Premature neonates: <24 days postnatal	1.0 mg/kg every 12 hrs	Dosage should be adjusted based on serum theophylline concentrations to obtain peak steady-state serum theophylline concentrations of 5-10 mg/L for neonates and 10-15 mg/L for infants and older children.
≥24 days postnatal	1.5 mg/kg every 12 hrs	
Full term infants up to 1yr	Total daily dosage (mg) = [(0.2 X age in weeks) + 5.0] x (body weight kg) ≤26 weeks; divided q8hrs >26 weeks; divided q6hrs	
Children 1 – 15 yrs[c] < 45kg	12 – 14 mg/kg/day divided q4-6hrs (Maximum: 300 mg/day)	After 3 days, if tolerated: 16 mg/kg/day divided q4-6hrs (Maximum: 400 mg/day) After 3 more days, if tolerated: 20 mg/kg/day divided q4-6hrs (Maximum: 600 mg/day)
Children 1 – 15 yrs[c] > 45kg and Adults (16 – 60 yrs)[d]	300 mg/day divided q6-8hrs	After 3 days, if tolerated: 400 mg/day divided q6-8hrs After 3 more days, if tolerated: 600 mg/day divided q6-8hrs

a. If trough concentrations are low before the next dose, then slow-release products may decrease the fluctuation and permit longer dosing intervals.
b. Products containing an aminophylline salt should divide the listed dose by 0.8.
c. Children 1 – 15 years of age, the initial theophylline dose should not exceed 16 mg/kg/day up to a maximum of 400mg/day in the presence of risk factors for reduced theophylline clearance or if not feasible to monitor serum theophylline concentrations.
d. In adolescents ≥ 16 years, the initial theophylline dose should not exceed 400mg/day in the presence of risk factors for reduced theophylline clearance or if not feasible to monitor serum theophylline concentrations.

Initial dosing using volume of distribution:

- Load dose: $X_o^* = C \times Vd$ Assume V = 0.5 L/kg

b. Concentration Predictions/Dosage Adjustments

S-R (e.g. Theodur)

$$\bar{c} = \frac{F \cdot S \cdot X_o}{Cl_s \cdot \tau}$$ S = 1; F = 1

Continuous infusion

$$\bar{c} = \frac{S \bullet K_o}{Cl_s}\left(1\text{-}e^{-Kt}\right)$$ S = 0.8, if aminophylline
K = Cl_s/V

$$\bar{c} = \frac{S \bullet K_o}{Cl_s}$$ at ss

The Chiou equation may be used to calculate Cl_s, prior to reaching ss. Basic assumptions: (1) known V; (2) true zero-order infusion between 2 sampling points (C_1 and C_2). Obtain two levels at 1 and 9h after starting infusion (optimally, one t 1/2 apart).

$$Cl_s = \frac{2 \cdot K_o \cdot 0.8}{C_1 + C_2} + \frac{2 \cdot V \cdot (C_1 - C_2)}{(C_1 + C_2) \cdot (t_2 - t_1)}$$

Oral (rapidly absorbed product)

$$C_{tr}^{ss} = C_{pk}^{ss} \cdot e^{-K\tau} = \frac{S \cdot F \cdot X_o}{V} \cdot e^{-K\tau} \cdot \left(\frac{1}{1\text{-}e^{-K\tau}}\right)$$

Changing from iv to oral S-R prep (e.g. Theodur)

Administer oral S-R prep; d/c IV 1 to 2 h later.

5. Selected factors altering theophylline clearance

Subpopulation	V L/kg	Cl (L/kg/h)	Cls* Factor	t½ (h)	Maintenance Dose (mg/kg/h)	
					Amino-phylline	Theo-phylline
AGE						
Nonsmoking adult	0.5	0.040	1.0	8.7	0.5	0.4
Premature infant (3-15 days)	0.7	0.018	0.4	12-48	0.2	0.16
Premature infant (25-57 days)		0.039	0.6	-	0.3	0.24
Infant (4-18 months)	0.56	0.089	2.0	4.8	1.0	0.8
Children (1-4 yrs)	0.48	0.100	2.0	3.4	1.0	0.8
Children (6-17 yrs)	0.46	0.087	1.6-2.0	3.7	0.8-1.0	0.64-0.8
Elderly (>65 yrs)	0.4-0.5	0.036-0.040	0.87-1.0	7.9-8.7	0.4-0.5	0.32-0.4
SMOKING						
cigarettes	0.5	0.064	1.6	5.4	0.8	0.64
marijuana	0.5	0.072	1.8	4.8	0.9	0.72
cigarettes / marijuana	0.5	0.090	2.2	3.8	1.1	0.88
DRUG						
cimetidine	0.5	0.025	0.6	13.9	0.3	0.24
erythromycin	0.5	0.028	0.7	12.4	0.35	0.28
phenobarbital	0.5	0.053	1.2	6.5	0.6	0.48
propranolol	0.5	0.030	0.6-0.8	10.8	0.3-0.4	0.24-0.32
DISEASE STATE						
cirrhosis (bilirubin <1.5)	0.6	0.033	0.8	13-17	0.35-0.4	0.28-0.32
cirrhosis (bilirubin >1.5)	0.6	0.011	0.25	41-55	0.13	0.1
congestive heart failure	0.5	0.016	0.4	12-24	0.2	0.16
cor pulmonale	0.5	0.016	0.4	22	0.2	0.16
pulmonary edema	0.56	0.017	0.4	22.9	0.2	0.16
viral respiratory illness with COPD, Pneumonia	0.5	0.015	0.4	23	0.2	0.16
severe obstructive pulmonary disease	0.6-0.9	0.032	0.8	13-19	0.4	0.32
		0.032				
WEIGHT						
obesity	0.5 Use IBW	0.04 Use IBW	1.0	8.7	0.5 Use IBW	0.4 Use IBW

****The product of all the factors that are present should be multiplied by the average clearance value (0.04 L/kg/h).***

6. Pediatric Guidelines

See dosing guidelines.

7. Suggested References for Influences of Pathophysiological States on Theophylline Kinetics

Age:

adults	Hendeles (1978) Am Rev Resp Dis 118:97. Powell (1978) Am Rev Resp Dis 118:229. Hendeles (1995) Pharmacotherapy 15(4):409-427
premature infants	Aranda (1976) NEJM 295:413. Giacoia (1976) J Pediatr 89:829.
infants	Rosen (1979) Pediatrics 64:248.
children	Loughnan (1976) J Pediatr 88:874. Ellis (1976) Pediatrics 58:542
elderly	Chandler (1988) J Geriatric Drug Ther (3:23)

Smoking:

Powell (1977) Am Rev Resp Dis 116:17
Jusko (1978) Clin Pharmacol Ther 24:400.

Drug:

cimetidine	Weinberger (1981) N Engl J Med 295:413. Jackson (1981) Am Rev Resp Dis 123:615. Reitberg (1981) Ann Intern Med 95:582.
erythromycin	Cummins (1977) Pediatrics 59:144. Prince (1981) J Allergy Clin Immunol 68:427. May (1982) J Clin Pharmacol 22:125.
propranolol	Conrad (1980) Clin Pharmacol Ther 28:463.
phenobarbital	Landay (1978) J Allergy Clin Immunol 62:27.

Disease State:

cirrhosis	Piafsky (1977) N Engl J Med 296:1495. Mangione (1978) Chest 73:616.
CHF/cor pulmonale	Jenne (1977) Am J Hosp pharm 34:408. Vicuna (1979) Br J Clin Pharmacol 7:33.
pulmonary edema	Piafsky (1977) Clin Pharmacol Ther 21:310.
viral illness	Chang (1978) Lancet 1:1132. Clark (1979) Lancet 1:492.
severe airway obstruction	Powell (1978) Am Rev Respir Dis 118:229.

Weight:

Obesity	Gal (1978) Clin Pharmacol Ther 23:438. Blouin (1980) Clin Pharmacol Ther 28:619.

VALPROIC ACID

1. Time of Sampling (*$101*)

   a. Relative to Dose

   - trough within 30 min prior to dose
   - at ss

2. Recommended Frequency of Sampling

   - Initially after reaching steady-state (usually 2-4 days)
   - After each dosage adjustment at ss
   - Sampling should always be done at the same time before a dose and before the same dose each day. (preferably before AM dose, due to effects of diurnal variation on clearance).

     Bauer (1985) Clin Pharmacol Ther 37:697.

3. Therapeutic Range

   - 50-100 mcg/ml
   - Utility of serum concentration monitoring for valproic acid (VPA) has not been fully determined. This is partially due to concentration-dependent protein binding. It also may take several weeks to achieve a therapeutic effect even after the patient has achieved ss within the therapeutic range. Continued anticonvulsant effects are also seen even after VPA is undetectable in the blood. Studies are controversial in determining an exact relationship between serum concentration and therapeutic effect or toxicity.

4. General Guidelines for Monitoring

   a. Initial Dosing

   - IV loading (see next page)
   - Empiric - 5-10 mg/kg/day
   - Should be given in divided doses, usually TID - due to short t 1/2 and to minimize GI side effects.
   - Utility of QD dosing has been documented, although many patients cannot tolerate the associated GI discomfort.
   - **Baseline and follow-up LFTs should be obtained to assess liver toxicity.**

Loading Doses for IV Valproic Acid (Depacon®)

IV Valproic Acid has been used in Europe since the 1980s; approved in USA in 1997.

Indicated as an intravenous alternative when oral administration of maintenance doses are temporarily not feasible. Not systemically studied as initial therapy. There are no established guidelines for the use of IV valproic acid as a loading dose.

Recommended doses from package insert: Complex partial seizures: 10-15 mg/kg/day, incr. 5 – 10 mg/kg/week with usually max ~ 60 mg/kg/day. Simple and complex absence seizures 15 mg/kg/day, increase 5 – 10 mg/kg/week.

Recommended infusion rate: No faster than 20mg/min.

Recent studies with IV loading doses:

Wheless, 1998	Loading doses of 15-45mg/kg (1050 – 3150mg/70kg) infused over 1 hour (max rate ~ 50mg/min) in epilepsy patients (n=25, ages 4-39 yrs) without active seizures. Average Cpk 10min post infusion: 71-277 (mean, 135.3±59.5ug/ml). No significant adverse effects observed except 1 patient with Cpk > 200ug/ml had mild sedation.
Venkataraman, 1999	Loading doses of ~25mg/kg infused at 3-6mg/kg per min (82-319 mg/min) in epilepsy patients (n=21, ages 2-54 yrs). Cpk 20min post infusion= 64-204.1ug/ml (mean 132.6ug/ml). Five patients had pain at site of injection due to high concentration of VPA in infusion fluid. Recommended minimal dilution 1:1 with D5W, NS or LR.
Hovinga, 1999	Three pediatric patients. Pt#1: 10yo, LD: 20mg/kg followed by 2mg/kg/h infusion; Cpk 1hr post = 69.2ug/ml; 4 hrs later = 40ug/ml. Pt#2: 8yo, LD 13.4mg/kg; Cpk 3hrs post = 33.3ug/ml. Pt#3: 34 months, LD = 20mg/kg over 30min; Cpk 7hrs post = 49ug/ml.
Chez, 1999	Three pediatric patients with status epilepticus. Pt#1: 22 months, 30mg/kg over 60min (no side effects); Cpk = 74.9ug/ml. Pt#2: 13 months, 30mg/kg; Cpk 1hr post = 33.9ug/ml additional 30mg/kg given; Cpk = 102.6ug/ml. Pt#3: 8yo: LD = 30mg/kg & MD = 30mg/kg IV q6; Cpk = 100ug/ml, then 2 hours post = 40ug/ml.
White, 1999	Case report in 11yo. LD = 30mg/kg (960mg) over 1hr. BP decr. (130/80 to 70/55) ~39min after start of infusion, respiratory depression, required intubation. Cpk 5hrs post = 104 ug/ml. BP stabilized 14 hrs later after pressor therapy.
Naritoku, 1999	Loading doses ~19.4±5.4mg/kg (range 10.6-27.8), ~1420±540mg (range 700-2800mg) at rates of 20-50mg/min in epilepsy patients (n=20, 52.8±23.5yrs). Reported N/V in 2 patients; decr. BP in one patient. Recommended 0.23L/kg (16.1L/70kg) for LD calculation.
Cloyd, 2003	Loading doses ~ 15mg/kg infused over 5 min (3mg/kg/min) or 10 min (6mg/kg/min) in 112 patients with epilepsy (mean age = 36±16 yrs; wt = 76.6±25 kg). Mean Vd ~ 0.2 L/kg (range 0.12 – 0.30 L/kg, ~20% CV) but determined with limited sampling strategy (6hrs post dose). Mean (%CV) Cmax at 1hr: C_{total} = 73.5 (22%) mg/L, C_{free} = 8.3 (46%) mg/L. **Authors recommend using Vd = 0.2 L/kg to estimate loading dose.**

b. Dosage Adjustments

- Increase dose by 5-10 mg/kg/day every 5-7 days until reach therapeutic effect
- usual maintenance dose: 15 mg/kg/day
- max dose: 60 mg/kg/day

5. Pediatric Guidelines

- dose: 10-60 mg/kg/day (avg. 30 mg/kg/d)
- t½ : 8-12 hours in neonates
  5-8 hours in children
- dosing interval:

syrup	q 4-6 h
caps	q 8 h
tabs	q 8-12 h

- 90% will have transient increase in LFTs (usually no more than 2x normal) - returns to normal with chronic dosing

6. Drug Interactions

- Anticonvulsant polytherapy makes achievement of therapeutic serum concentrations of valproic acid very difficult. Carbamazepine, phenytoin, and phenobarbital all induce the metabolism of VPA (↑ Cl). Sackellares. (1981) Epilepsia 22:437.
- VPA ↓ s clearance of phenobarbital. Kapetanovic. (1981) Clin Pharmacol Ther 29:480.
- VPA displaces phenytoin from protein binding sites
  - initially, see ↑ f, ↓ C_T.
- VPA also inhibits phenytoin metabolism - with chronic dosing, see ↓ Cl_I and a rise in C_T to approximate C_T prior to VPA therapy. Monks. (1980) Clin Pharmacol Ther. 27:89. Bruni. (1980) Neurology 30:1233.
- Cimetidine inhibits the metabolism of VPA (i.e. up to 20% ↓ in Cl of VPA).
- Webster (1984) Eur J Clin Pharmacol. 27:341.

7. Dosage Forms

Syrup - sodium valproate (Depakene)	250mg/5ml
Capsules - valproic acid (Depakene)	250mg
Enteric coated tablets - divalproex sodium (Depakote)	125,250,500mg
Divalproex sprinkle capsules	125mg
Valproate sodium injection - (Depacon®)	100mg/ml (5ml vial)

- No difference in bioavailability (as measured by AUC) between the three products. Only difference is in the time to peak for each product.

syrup	2 hours
capsules	3-4 hours
tablets	3-8 hours

- Food delays the absorption of all three products.

8. Miscellaneous

- t½ — 8-17 h (↑ in hepatic disease, but questionable clinical significance).

- Vd — 0.15 L/Kg (range 0.13-0.23 L/Kg)

- f — variable; concentration-dependent (with ↑ conc, see ↑ f)
  clinical significance of variability unknown
  at 50 mcg/ml, f ≅ 0.05-0.1
  at 70 mcg/ml, f ≅ 0.2
  also affected by disease states (decreased protein binding)
  renal failure - f = 0.18.

  Gugler. (1978) Br J Clin Pharmacol. 5:44l.
  liver failure - f = 0.29

  Klotz (1978) Eur J Clin Pharmacol. 13:55
  hypoalbuminemia - f increased depending on severity

- elderly — ↑ f
  ↓ Cl

  Perucca. (1984) Brit J Clin Pharmacol. 17:665.

9. Other Suggested References

Applied Pharmacokinetics. (1986), 2nd ed., p. 540-69

Rectal Admin: Thorpy. (1980) Neurology. 30:1113.
Cloyd. (1981) Neurology. 31:1348.

General Review: Rimmer. (1985) Pharmacotherapy. 5:171.

FREE VALPROIC ACID

NOTE: ***Free valproic acid concentrations are sent to an outside laboratory; allow 2-3 days for reporting.***

Policy:

1. Any medical (or surgical or other) service can order free valproic levels if patients meet criteria in Appendix II.

2. Physicians on the Neurology service can request or interpret their own results, although the Clinical Pharmacokinetics Service will provide clinical interpretation if consulted.

3. For services other than Neurology, the following will apply:

   Once the TDM Lab receives a request for a free valproic acid level, TDM Lab will notify the pharmacist on that service or contact the Clinical Pharmacokinetics Service (for uncovered services). The Pharm.D. will monitor the criteria and provide essential clinical input regarding the need for the level.

   The pharmacist should make sure that a total concentration, as well as the free valproic acid concentration, is ordered.

   The pharmacist will notify TDM Lab if the assay should be run or cancelled. If an order is to be cancelled, the pharmacist needs to notify the physician first and document (in the patient's chart) the recommendation to cancel the concentration.

4. The therapeutic range of free valproic acid concentrations will be reported as 2.5 to 11.0 mcg/ml.*

Appendix II

Free valproic acid concentrations should be reserved for the situations described below. For example, a "normal" patient with normal albumin and normal renal function who is not on concurrent medications (that alter valproic acid protein binding or clearance) would not warrant a free valproic acid concentration.

A free valproic acid concentration is warranted when:

g. The total valproic acid dosage is >60 mg/kg/day.

OR

h. A patient is seizure-free at a total level of <50 mcg/ml and you need to determine whether a dosage increase is necessary.

OR

1. A patient is exhibiting signs of toxicity at a dosage of ≤60 mg/kg/day.

OR

i. A patient is in a unique subpopulation (e.g. a pregnant female, a patient on multiple anticonvulsant therapy, etc.)

VANCOMYCIN

1. Time of Sampling (*$137*)

   Relative to Dose

   - ***Verify that the patient will be approved to receive vancomycin beyond 72 hours (automatic stop date; see UK Hospital Vancomycin Policy) BEFORE ORDERING CONCENTRATIONS***
   - peak at 1 h after end of 1h infusion
   - trough within 30 min prior to dose
   - at ss (24 to 30 hours after initiation of therapy) usually around third maintenance dose (or later), preferably during day

2. Recommended Frequency of Sampling (Approved by Antimicrobial Subcommittee)

   Patients in whom vancomycin serum drug concentrations should NOT be obtained:

   - Adult patients < 60yo with normal body weight, stable renal function with Clcr > 40 ml/min, and short course of therapy (e.g., <7 days)

   Patients in whom ONLY TROUGH vancomycin serum concentrations should be obtained:

   - Patients on vancomycin ≥ 7 days
   - Renal impairment – estimated Clcr < 40ml/min
   - Changing renal function defined by increase in serum creatinine by 0.5 mg/dL or 50% from baseline
   - Special patient populations with altered volume distribution or renal clearance including:
     - Elderly: ≥ 60 years old
     - Burn
     - Cancer
     - Obesity > 125% ideal body weight
     - Pediatric
   - Concomitant nephrotoxic drugs including:
     - Aminoglycosides
     - Amphotericin B
     - Loop diuretics
     - Vasopressor agents
     - Others (IV contrast dye, ACE inhibitors)

   Patients in whom peak and trough serum drug concentrations should be obtained:

   - Higher doses of vancomycin required to penetrate site of infection or treatment of serious life-threatening infections including:
     - Meningitis
     - Endocarditis
     - Pneumonia
     - Sepsis

3. Therapeutic Range*

- Peak: 20 – 40 µg/mL (at 1hr after end of 1hr infusion)
  Target peaks should be approx. 8xMIC and troughs 1-2xMIC of organism.
- Trough: 5 – 15 µg/mL
  Vancomycin troughs of 15-20 mg/L may be warranted for life-threatening infections, organisms with high MICs (e.g., MRSA), or to ensure vancomycin concentration at the site of infection.

Zimmermann AE; Katona BG; Plaisance KI. Association of vancomycin serum concentrations with outcomes in patients with gram-positive bacteremia. *Pharmacotherapy* 1995 Jan-Feb;15(1):85-91.

Karam CM, McKinnon PS, Neuhauser MM, Rybak MJ. Outcome assessment of minimizing vancomycin monitoring and dosing adjustments. *Pharmacotherapy* 1999 Mar;19(3):257-66.

4. General Guidelines for Dosing and Monitoring

a. Initial Loading Dose (20-25 mg/kg)

- 20-25 mg/kg based on ABW (see weight range recommendations)
  - 40-60 kg = 1000 mg IV x1
  - 61-80 kg = 1500 mg IV x1
  - > 80 kg = 2000 mg IV x1

b. Initial Maintenance Dose

- **Modified Matzke Nomogram: Dose = 15 mg/kg using ABW and Dosing Interval (τ) should maintatin serum trough concentrations of 12.5 mcg/ml. Each dose should be infused over at least 1 hour.**

Nomogram* for vancomycin in patients with various degrees of renal function		
Creatinine Clearance (mL/min)	**Dosing interval (τ) DAYS**	**Dosing interval (τ) HOURS**
120	0.35	8-12
100	0.5	12
80	0.5	12
60	0.75	18
40	1.0	24
30	1.5	36
20	2.0	48
10	4.0	-
5	6	-
0	12	-
Hemodialysis	*Not significantly removed by conventional hemodialysis. Initial dose = 20-25 mg/kg then suggest checking "random" serum concentration in 3-4 days. Redose with 15mg/kg when concentration is 15mg/L.*	

*Adapted from Matzke GR, et al. *Antimicrob Agents Chemother*. 1984 Apr;25(4):433-7.

- For **<u>morbidly obese patients</u>** (> 90% over their IBW) with **<u>normal renal function</u>**: **15mg/kg/dose X ABW every 12 hours**.

  NOTE: *Obese patients may require larger total daily doses at less frequent intervals (i.e., q8hrs) in order to avoid low trough concentrations for prolonged periods.*

  *Bauer LA; Black DJ; Lill JS. Vancomycin dosing in morbidly obese patients. *Eur J Clin Pharmacol* 1998 Oct;54(8):621-5

- For **<u>morbidly obese patients</u>** with **<u>renal insufficiency</u>** (*estimated Clcr using the Salazar-Corcoran equation*): Use **15mg/kg X ABW every** τ determined from the table above (Matzke nomogram)

Alternative dosing method using estimated pharmacokinetic parameters (Vd and K) and Sawchuk-Zaske Method (refer to aminoglycoside section for equations):

Normal Vd range: 0.5 – 0.9 L/kg (use average 0.7 L/kg)

Estimate K using Clcr: **K (hr^{-1}) = 0.00083 (Clcr) + 0.0044** (Matzke)

c. <u>Dosage Adjustments Using Sawchuk-Zaske Method:</u>

Assumptions: Samples obtained correctly at steady-state; 1-compartment model; principle of superposition; linear elimination.

1. Verify administration and sampling times.
2. Calculate K:

$$K = \frac{\ln\left(\frac{C_{pk}^{ss}}{C_{tr}^{ss}}\right)}{T'}$$

T' is determined by subtracting the time difference between Cpk and Ctr from the Tau. For example, if the time difference between Cpk and Ctr was 1.5hrs and the Tau = q8hrs, then T' = (8 - 1.5) = 6.5hrs.

3. Calculate t½:

$$t_{½} = \frac{0.693}{K}$$

4. IF peak concentration is drawn late, calculate if drawn at correct time:

$$C_{pk}^{ss} = \frac{C_{pk}}{e^{-Kt'}}$$

where C_{pk}^{ss} = peak concentration drawn at appropriate time;

C_{pk} = peak concentration drawn late; t' = time between late C_{pk} and C_{pk}^{ss}

5. IF trough concentration is drawn early (e.g., >30min prior to dose), calculate if drawn at correct time:

   $C_{tr}^{ss} = C_{tr} * e^{-Kt'}$

   where C_{tr}^{ss} = trough concentration drawn at appropriate time

   (e.g., suggest use dose administration time)

   C_{tr} = trough concentration drawn early; t' = time between early C_{tr} and C_{tr}^{ss}

6. Calculate Vd:

   If doses have reached **steady state** (e.g., previous doses on time, concentrations drawn appropriately), use:

$$Vd = \frac{K_o(1-e^{-Kt})\,e^{-KT}}{C_{pk}^{ss} \cdot K\,(1-e^{-K\tau})}$$

t = infusion time (e.g., 1hr)

T = time between end of infusion & C_{pk}^{ss} (e.g., 1hr)

   If doses have **NOT** reached **steady state <u>AND</u>** there are at least 3 concentrations after a multiple dose (e.g., trough, peak, & random) or 2 concentrations after the 1st dose (e.g., peak and random or 2 random concentrations) use:

$$Vd = \frac{K_o(1-e^{-Kt})}{K\,(C_{pk}^{max} - C_{tr}e^{-Kt'})}$$

C_{pk}^{max} = peak extrapolated to END of infusion
t = time of infusion
t' = time between C_{tr} and C_{pk}^{max}

   To use above equation, calculate peak at end of infusion:

$$C_{pk}^{max} = \frac{C_{pk}}{e^{-KT}}$$

T = time between C_{pk} and C_{pk}^{max}

7. IF measured C_{tr} is high, calculate time required to achieve desired C_{tr}:

$$t' = \frac{\ln\left(Ctr_1 / Ctr_2\right)}{K}$$

Ctr_1 = high Ctr; Ctr_2 = desired Ctr

t' = time required from Ctr_1 to Ctr_2

8. Calculate new dosing interval (τ):

$$\tau = \frac{\ln(C_{pk}/C_{tr})}{K} + t + T$$

t = infusion time (e.g., 1hr)

T = time between end of infusion & C_{pk} (e.g., 1hr)

9. Calculate new dosing rate:

$$K_o = \frac{C_{pk}^{ss}\ Vd\ K(1-e^{-K\tau})}{(1-e^{-Kt})\ e^{-KT}}$$

t = infusion time (e.g., 1hr)

T = time between end of infusion & C_{pk} (e.g., 1hr)

10. Round dose to nearest 10mg or available stock bag dose (80,100,120mg) then recalculate the actual C_{pk}:

$$\text{desired } C_{pk}\ X\ \frac{\text{actual (rounded) dose}}{\text{calculated dose}} = \text{actual } C_{pk}$$

11. Estimate trough to be obtained with above K_o and τ:

$$C_{tr}^{ss} = C_{pk}^{ss} e^{-KT'}$$

12. Document the pharmacokinetic assessment in the medical records.

    WRITE A CHART NOTE. Document pertinent clinical monitoring parameters, dose recommendations and estimated and/or calculated pharmacokinetic parameters in the medical record. (*Also refer to Department of Pharmacy Guidelines for Writing Notes in Patient Charts, PH-02-04*)

    - Briefly describe the rationale of the drug and determine if warranted based on clinical and patient information. Refer to UK Hospital guidelines for appropriate use of vancomycin.
    - Document the current day of therapy and goal length of therapy (e.g., Day #2/14 vancomycin), and any concomitant antibiotics.
    - Document the collect times of the reported concentrations and note if the samples were obtained appropriately. For example, if actual C_{pk} was drawn late, <u>also</u> document the estimated C_{pk} if drawn correctly.
    - Include the calculate PK parameters: K (hr^{-1}), t½ (hrs), Vd (L) <u>and</u> Vd (L/kg – DBW).
    - Write a new dosage in mg and mg/kg-DBW/dose (e.g., vancomycin 1000 mg IV q12hrs, 15mg/kg/dose).
    - When changing a dosage, include the start time of new dosing regimen with the order (*very helpful for the pharmacist entering the order and the nurse administering the drug*).
    - Include a range for the predicted concentrations with the new dosage recommendation: (e.g., C_{pk} = 8-10mg/L; C_{tr} <2mg/L, ~1mg/L).
    - Include other pertinent information used to assess the patient: weight (ABW, IBW, DBW), height, BSA, Scr, Clcr, BUN, urine output, I/Os, cultures, Tmax, WBC, differential, allergies, and other nephrotoxic medications (e.g., furosemide, amphotericin, aminoglycosides).
    - Refer to the sample note on the next page.

Sample Note

PHYSICAL / HISTORY / PROGRESS NOTES

Patient Name:
Medical Record:
Date of Birth:

Date	Clinical Pharmacokinetics Service RE: Vancomycin Day #2/14
9/2/2001 14:30 ABW = 80kg Ht = 6'0" IBW = 77.6kg Scr = 1.2 (today) Clcr = 93ml/min	Patient is 40yo WM being treated with vancomycin 1000mg IV q12hrs (12.5 mg/kg/dose) for staphylococcal bacteremia based on positive blood cultures (9/1, both bottles) for *Staphylococcus aureus*. Current Tmax 102.5, WBC = 15K. Vancomycin therapy meets approval criteria. ID service is following patient and recommends Cpk ~ 35-40mg/L and Ctr = 10-15 mg/L (discussed with ID resident). Vancomycin concs drawn around 3rd dose on 9/2: Trough = 8.7 mg/L C: 07:30 Dose = 1200 mg IV infused from 08:00 – 09:00 Peak = 22 mg/L C: 11:00 Assessment of concs: Previous doses administered on time & represent steady-state; Ctr drawn appropriately; Cpk drawn 1hr late & if drawn correctly @ 10:00 = 24.6 mg/L; Cpk and Ctr below recommended range. Renal function stable. PK parameters: K = 0.11hr^{-1}; t½ = 6.3 hrs; Vd = 47.1L (0.6 L/kg) Recommendations: 1. Suggest changing vancomycin to 1500mg IV q12hrs (18.75 mg/kg/dose) to yield a Cpk ~35-40 mg/L & Ctr ~ 12mg/L; begin next dose at scheduled time (9/2 @ 20:00); discussed with ID resident and primary team. 2. Not necessary to recheck Cpk & Ctr unless change in clinical status or renal function; if continue therapy > 7 days, would suggest checking Ctr each week to assess for drug accumulation. 3. Suggest checking Scr/BUN at least 2X/week to assess renal function.

1. Pediatric Guidelines

Empirical dosing administration guidelines for vancomycin in neonates, infants, and children[#]		
Postconceptional age	*Bodyweight*	*Dose*[*#]*
< 27 weeks	< 800 grams	18 mg/kg q36 hrs
27-30 weeks	800-1200 grams	16 mg/kg q24 hrs
31-36 weeks	1200-2000 grams	18 mg/kg q12 hrs
>36 weeks & postnatal age < 7 days	>2000 grams	15mg/kg q12 hrs
>36 weeks & postnatal age 8-30 days	>2000 grams	15mg/kg q8 hrs
>36 weeks & postnatal age >30 days	>2000 grams	10mg/kg q6 hrs
Infants > 1month and children	30-40mg/kg/day in divided doses every 6-8 hrs	
For CNS infections	*60mg/kg/day in divided doses every 6-8 hrs*	

*Dosing interval should be extended in renal impairment; [#]parenteral administration of vancomycin should be administered over at least 60 minutes at a final concentration <5mg/mL; CNS = central nervous system

[#]Rodvold KA, Everett JA, Pryla RD, Kraus DM. Pharmacokinetics and administration regimens of vancomycin in neonates, infants, and children. *Clin Pharmacokinet* 1997;33(1):32-51.

2. Vancomycin- Hemodialysis

Dose
1. Loading dose of 15mg/kg based on ABW

Effect of hemodialysis
1. Not significantly dialyzed by conventional low-flux dialysis less than 10% of total body stores removed over a 3-4 hour hemodialysis session.
2. When high-flux filter is used serum concentrations decrease by 1/3 but slowly rebound to 90% of pre-dialysis levels over 10-12 hours.
2. Elimination primarly due to residual kidney function of patient. Limited extrarenal mechanisms of elimination.
3. Average half-life in ESRD patients is 4-5 days depending on residual kidney function.

Levels
1. Levels are usually drawn 3-5 days post-dose labeled as a random level.
2. Redose when level is expected to be $\leq$ 15 mg/L.
3. Levels drawn 10-12 hours following high-flux hemodialysis may be misleading. Obtaining level prior to hemodialysis is preferred.

References (Drug dosing in renal failure/dialysis):
1. National Kidney Foundation, Kidney Disease Outcomes Quality Initiative; Clinical Practice Guideline for Chronic Kidney Disease. www.KDOQI.org.
2. Bauer LA. *Applied Clinical Pharmacokinetics*. United States: McGraw Hill; 2001.
3. Aronoff GR, Berns JS, Brier ME, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults.* 10th ed. Philidelphia, PA:American College of Physicians:1999.

3. Suggested References for Influences of Pathophysiologic States on Vancomycin Kinetics

Infants and Children: Schaad (1980) J Pediatrics 96:119-126.

Elderly: Cutler (1984) Clin Pharmacol Ther 36:803-810.

Obesity: Blouin (1982) Antimicr Ag Chemother 21:575-580.

Burn Patients: Brater (1986) Clin Pharmacol Ther 39:631-634.

Critically Ill Patients: Garaud (1984) J Antimicrob Chemother 14 (Suppl D):53-57.

4. Other Suggested Readings

1. Karam C., McKinnon P., et al. Outcome assessment of minimizing vancomycin monitoring & dosing adjustment. Pharmacotherapy 9(3);1999:257-66.
2. Cohen E., Dadasher A., Drucker M., et al. Once daily vs. twice daily IV administration of Vancomycin for infections in hospitalized patients. J. Antimicobial Chemotherapy 49; 2002:155-60.

3. Zimmerman A., Katona B., Plaisance K. Association of vancomycin serum concentrations with outcomes in patients with gram-positive bacteremia. Pharmacotherapy 15(1);1995:85-91.
4. Cantu T., Yamanaka-Yuen N., Lietman P. Serum vancomycin concentration: reappraisal of their clinical value. Clin Infect Dis 18;1994:533-43.
5. Moellering Robert Jr. Editorial: Monitoring serum vancomycin levels: Climbing the mountain because it is there? Clin Infect Dis 18;1994:544-6.
6. Leader W., Chandler M., Castiglia M. Pharmacokinetic Optimisation of Vancomycin Therapy. Clin Pharmacokinetics 28(4);1995:327-342.
7. Hammett-Stabler C., Johns T. Laboratory guidelines for monitoring of antimicrobial drugs. Clin Chem 44;1998:1129-1140.
8. Palmer-Toy D. Therapeutic monitoring of vancomycin. Arch Pathol Lab Med 124;Feb2002:322-3.
9. Matzke GR, McGory RW, Halstenson CE, Keane WF. Pharmacokinetics of vancomycin in patients with various degrees of renal function. Antimicrob Agents Chemother 1984 Apr;25(4):433-7.

GUIDELINES FOR SALIVA MONITORING

Provided by Melody Ryan, Pharm.D.
Assistant Professor, College of Pharmacy & Department of Neurology

Saliva Antiepileptic Monitoring

- Saliva monitoring is available for carbamazepine, phenobarbital, and phenytoin

Drug	Therapeutic Range	Interpretation
Carbamazepine	1.4 - 3.5 μg/mL	Use C-bar equation
Phenobarbital	5 - 15 μg/mL	Use C-bar equation
Phenytoin	1 – 2 μg/mL	Same as free phenytoin

Saliva should NOT be used when

- Patients need a STAT concentration
  - It takes about two hours to get results from saliva testing
- Patients took their dose of carbamazepine, phenobarbital, or phenytoin in the last 3 hours
- Patients who have eaten or drunk anything but water in the last 15 minutes

Ordering the test

- Write **"saliva phenobarbital" or "saliva carbamazepine" or "saliva phenytoin**" on Lab Miscellaneous form

Collecting the saliva

- It is important to remember that saliva, not sputum, needs to be collected
  - If the patient is able to follow directions, he/she should be asked to spit in a 5 dram vial. This should be the saliva collected in the mouth (i.e., nothing from the lungs)
  - If the patient is unable to follow directions, the saliva can be collected with a disposable plastic pipette directly from the mouth to the 5 dram vial.
  - Do NOT use a suction tube to collect a sputum specimen
- Saliva Collection Packets can be obtained from Special Chemistry (3-6093) and contain a 5 dram vial and a premarked disposable pipette in a Ziploc bag.
- At least 0.5 mL of saliva needs to be collected.
- Cap the vial and label it with the addressograph label
- Deliver the specimen to the laboratory using the usual means.

Helpful tips

- If the patient is having difficulty producing saliva, have him/her think about food and/or make chewing motions with his/her mouth
- For infants, tilting the head sideways will cause saliva to pool in the cheek pocket. It is then easier to collect the sample
- When collecting saliva directly from the mouth, be careful that the patient doesn't bite you

Result reporting

- Results are reported routinely in Clinipac and Sunrise Clinical Viewer at the completion of the analysis (approximately 2 hours).

Suggested References

1. Anavekar SN, Saunders RH, Wardell WM, et. al. Parotid and whole saliva in the prediction of serum total and free phenytoin concentrations. *Clin Pharmacol Ther* 1978;24:629-37.
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Guide to Anticoagulation (Revised 06/07)

For Inpatient Questions between 0800-1700 Monday to Friday
Page PharmD on Service or Anticoagulation Management Service pager 4331

For Inpatient Questions after hours please page PharmD on call pager 1875

References (Warfarin)
1. Seventh ACCP Consensus Conference on Antithrombotic Therapy. Chest 2004; 126(3): [Supp 1] 204S-33S.
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References (Heparin/Enoxaparin)
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Additional references available upon request.

Warfarin

Mechanism of Action:

- Inhibits reduction of vitamin K epoxide, thereby limiting activation of vitamin K dependent clotting factors: II (prothrombin), VII, IX, X. *Antithrombotic effect primarily due to reduction in prothrombin.*
- Inhibits synthesis of anticoagulant proteins C and S (potential procoagulant effects).

Pharmacokinetics:

Warfarin is a racemic mixture of two active isomers, R and S. The S-isomer is approximately five times more potent than the R-isomer.

Oral Administration

Absorption: rapidly and completely absorbed

Distribution: primarily intravascular, highly protein bound

Half-life: 36-42 hours

- Time to steady state = approximately 10 days

Half-lives of Clotting Factors:

Factor II = 60 hrs
Factor VII =6 hrs
Factor IX = 24 hrs
Factor X = 40 hrs

Anticoagulation may be seen within 24 hours due to inhibition of Factor VII, but peak anticoagulant activity is delayed for 72-96 hours due to Factor II inhibition (2-3 days after 1st therapeutic INR)

Metabolism: Hepatic microsomal enzymes to inactive metabolites

- S-isomer is metabolized primarily by cytochrome P450 (CYP) 2C9
- R-isomer is metabolized by CYP 1A2 and CYP 3A4
- Reduce dose with hepatic dysfunction and with hypermetabolic states (increased catabolism of vitamin-K dependent factors)
- Not significantly affected by dialysis

Dosing and Monitoring:

Dose that is required is variable and dependent on a number of patient-specific and environmental factors. Refer to dosing guidelines on following page.

Recommend collecting baseline INR prior to warfarin initiation to assess sensitivity. Collect INR daily in hospitalized patients being initiated on warfarin until INR is within the desired therapeutic range, then two or three times weekly.

Warfarin Anticoagulation Initiation Dosing for Warfarin Naïve Patients

Day	INR	Warfarin High Sensitivity*	Warfarin Moderate Sensitivity**	Warfarin Low Sensitivity***
1	Baseline INR	2.5-5 mg	7.5 mg	10 mg
2	<1.5	2.5-5 mg	7.5 mg	7.5-10 mg
	1.5-1.9	2.5 mg	2.5 mg	2.5 mg
	2-2.5	1-2.5 mg	1-2.5 mg	1-2.5 mg
	>2.5	0	0	0

Continue for all patients

Day	INR	Dose
3	<1.5	5-10 mg
	1.5-1.9	2.5-5 mg
	2-2.5	0-2.5 mg
	2.6-3	0-2.5 mg
	>3	0
4	<1.5	10 mg
	1.5-1.9	5-7.5 mg
	2-3	2.5-5 mg
	>3	0-2.5 mg
5	<1.5	10 mg
	1.5-1.9	7.5-10 mg
	2-3	2.5-5 mg
	>3	0-2.5 mg
6	<1.5	7.5-12.5 mg
	1.5-1.9	5-10 mg
	2-3	2.5-5 mg
	>3	0-2.5 mg
7	Make adjustment based on total weekly dose (Increase or decrease dose by 5-20% depending on current INR and target INR)	

*High Sensitivity	**Moderate Sensitivity	***Low Sensitivity
Baseline INR >1.5	Baseline INR 1.2-1.5	Baseline INR <1.2
>65 years of age	50-65 years of age	<50 years of age and no other risk factors
Significant hepatic disease	Concurrent CYP-450 hepatic enzyme inhibitor (see table for details)	
Decompensated CHF		
Malnourished		
Malabsorption syndrome/ chronic diarrhea		
Cancer		
Hypoalbuminemia (esp<2)		
Thyrotoxicosis		
Genetic polymorphism of CYP-450 2C9		

Adverse reactions

Warfarin:

- Over Anticoagulation / Bleeding

Guidelines on Vitamin K_1 Administration for Reversal of Warfarin

INR	Action/Recommendation
Greater than therapeutic but < 5 with no significant bleeding	Continue with lower warfarin dose, OR omit a dose and resume therapy at a lower dose.
5-9 (No significant bleeding)	Omit 1 or 2 doses (monitoring INR more frequently), and resume therapy at a lower dose when INR therapeutic,
OR	
If patient is at risk of bleeding	omit a dose and administer vitamin K_1 1.25 to 2.5 mg PO
5-9 (Rapid reversal required for urgent surgery)*	Administer vitamin K_1 2.5 mg PO (INR to normalize in 24 hours); if INR still high, administer additional 1.25 to 2.5mg of vitamin K_1 PO.
>9 (No significant bleeding)	Hold warfarin therapy AND administer vitamin K_1 5-10 mg PO, administer additional vitamin K_1 in 24-48 hours if necessary; resume therapy at a lower dose when INR therapeutic.
Significant bleeding at any INR value	Hold warfarin therapy AND administer vitamin K_1 10 mg by slow IV infusion (1mg/min) diluted in D5W or NS; may repeat every 12 hours if needed. (Supplement with fresh frozen plasma, depending on urgency)
Life threatening bleeding	Hold warfarin therapy AND administer fresh frozen plasma AND administer vitamin K_1 10 mg by slow IV infusion (1mg/min) diluted in D5W or NS.

*For patients with INR >1.5 but <5 requiring reversal for urgent surgery administer vitamin K_1 1.25 to 2.5 mg PO, or for patients NPO, 1 mg IV.

Selected Factors Altering Warfarin Pharmacokinetics and Pharmacodynamics

Increased Warfarin effect
Acetaminophen (high doses)
Alcohol (acute ingestion)
Aminosalicylic acid
Allopurinol
Amiodarone
Aspirin
Cimetidine
Ciprofloxacin
Clarithromycin
Dexamethasone (≥20 mg)
Disulfiram
Erythromycin
Fluconazole
Flu vaccine
Itraconazole
Isoniazid (600 mg/day)
Levothyroxine
Metronidazole
Omeprazole
Phenytoin (long term)
Propoxyphene
Quinidine
Sulfonylurea
Tamoxifen
Tetracycline
TMP/SMX

Decrease Warfarin effect
Alcohol (chronic ingestion)
Aminoglutethimide
Barbiturates
Carbamazepine
Cholestyramine
Dicloxacillin
Griseofulvin
Nafcillin
Phenytoin
Rifampin
Sucralfate
Vitamin K

Increased Bleeding
Aspirin
NSAIDs

Ticlopidine
Clopidogrel

Thrombocytopenia

Optimal Therapeutic Range for Oral Anticoagulation

Indication	INR
Atrial Fibrillation	
Atrial Fibrillation with high risk factors (age >75 years, history of TIA or stroke, hypertension, history systemic embolus, mitral stenosis, bioprosthetic cardiac valve, thyrotoxicosis, left ventricular dysfunction, CHF, rheumatic mitral valve disease)	2-3 (chronic)
Atrial Fibrillation with ≥ 2 moderate risk factors (Age 65-75 years, diabetes mellitus, coronary artery disease)	2-3 (chronic)
Pre-cardioversion (for Afib >48 hours)	2-3 (3 weeks)
Post-cardioversion	2-3 (4 weeks)
Cardioembolic Stoke	2-3 (chronic)
Left Ventricular Dysfunction	
Ejection Fraction < 30%	2-3 (chronic)
Following embolic event despite anticoagulation	2-3 (chronic) plus ASA 81 mg qd
Myocardial Infarction (MI)	
Following anterior MI	2-3 (1-3 months)
Following MI with continued risk factors (Afib, LV dysfunction, CHF, mural thrombosis, history of embolism)	2-3 (chronic)
Thromboembolism (DVT, PE)	
Treatment/prevention of recurrence (reversible or time-limited risk factors)	2-3 (3 months)
Treatment/prevention of recurrence (first episode of idiopathic thrombus)	2-3 (6 months)
Continued presence of risk factors (AT-III, protein C or S deficiency, malignancy)	2-3 (12 months-chronic)
Symptomatic calf vein thrombosis	2-3 (6-12 weeks)
Prophylaxis of venous thrombosis (high risk surgery)	2-3

Optimal Therapeutic Range for Oral Anticoagulation

Indication	INR
Valvular Disease	
Aortic valve disease	
with concurrent mitral valve disease	2-3 (chronic)
with associated atrial fibrillation	2-3 (chronic)
Mitral annular calcification	
with associated atrial fibrillation	2-3 (chronic)
with history of systemic embolization	2-3 (chronic)
Mitral valve prolapse	
with associated atrial fibrillation	2-3 (chronic)
with history of systemic embolization	2-3 (chronic)
with history of TIA despite Aspirin therapy	2-3 (chronic)
s/p embolic event despite anticoagulation	2-3 (chronic) plus ASA 325 mg qd
Patent foramen ovale/atrial septal anuerysm	
with history of systemic embolization	2-3 (chronic)
with history of TIA	2-3 (chronic)
Rheumatic mitral valve disease	
with left atrial diameter > 5.5 cm	2-3 (chronic)
with associated atrial fibrillation	2-3 (chronic)
with history of systemic embolization	2-3 (chronic)
s/p embolic event despite anticoagulation	2.5-3.5 (chronic) or 2-3 (chronic) plus ASA 81 mg qd or clopidogrel 75mg qd
Valve Replacement	
Mechanical valve prosthesis (tilting disk valves, bileaflet mechanical valves in the mitral position or aortic position with atrial fibrillation)	2.5-3.5 (chronic)
Bileaftet aortic mechanical valve (provided normal sinus rhythm, normal ejection fraction, and normal sized atrium)	2-3 (chronic)
Mechanical valve following systemic embolization or risk factors (Concurrent atrial fibrillation, history of systemic embolization left atrial thrombus, severe left ventricular dysfunction)	2.5-3.5(chronic) plus ASA 81 mg qd
Tissue valve prosthesis	2-3 (3 months)
Tissue valve with history of systemic embolization	2.5-3 (3-12 months)
Tissue valve with atrial fibrillation or pacemaker	2-3 (chronic)

Sample of Documentation Template for Warfarin

UNIVERSITY OF KENTUCKY HOSPITAL
KENTUCKY CLINIC
LEXINGTON, KENTUCKY

HISTORY/PHYSICAL/ PROGRESS NOTES

Patient Name:

Medical Record #:

Date of Birth:

HPI:

ABW: **Height:** **IBW:**

PMHx:

Social Hx: **EtOH:** **Tobacco:**

Current Medications:

Indication for Anticoagulation:
Target INR: **Expected Duration:** **Start Date:**

Anticoagulation History:
Previously on warfarin *YES/NO* **Dates:** **Previous Indication:**
Previous warfarin maintenance dose:

Other information:

Hospital Anticoagulation:

Date												
INR												
Warfarin Dose (mg)												

Labs: (CBC, LFTs)
HCT: **HGB:** **PLT:** **LFTs**

Anticoagulation Assessment/Recommendation (include evaluation of potential drug-drug interactions):

Initial warfarin teaching: *Done/Not Done/Date to be Done:*
Healthcare Provider to manage warfarin after discharge: **Contact Info:**

Name (#Beeper)
_____

Unfractionated Heparin

Mechanism of Action

- Binds to and causes conformational change in anti-thrombin III thereby accelerating inactivation of activated clotting factors IIa (thrombin), IXa, Xa, XIa and XIIa, subsequently halting coagulation.
- Low dose predominantly affects factor Xa (prophylaxis)
- Full-dose predominantly affects factor IIa (thrombin) (established clot)

Pharmacokinetics

Unfractionated Heparin (IV or SQ):

Absorption (SQ): completely absorbed (at treatment doses); peak concentrations at 2-4 hrs

Distribution: primarily intravascular

Half-life: 90 minutes (range 0.5-2 hours)

- Mean time to steady state = 6 hours (3-5 half-lives)
- Increases with larger doses (non-linear)
- Decreases with PE, massive thrombus, or new clot (increased clearance)

Metabolism: degraded by reticuloendothelial system

- No dose adjustment necessary for hepatic or renal dysfunction
- Not significantly affected by dialysis

Prophylaxis Dosing

General Surgery / Medicine Patients

- Unfractionated heparin (UFH) 5000 units sq q8h or q12h

Treatment (initial dosing)

General Considerations

- Initial doses based on using actual body weight
- See heparin protocol for additional dosing adjustment and monitoring recommendations

Management of venous thromboembolis (VTE)/ pulmonary embolism (PE)

- UFH 80 units/kg (bolus), not to exceed 10,000 units.
- UFH 18 units/kg/hr (maintenance), max initial infusion rate 2,000 units/hr, titrate to goal aPTT.

Acute Coronary Syndrome (ACS)

- UFH 70 units/kg (bolus), not to exceed 5,000 units
- UFH 15 units/kg/hr infusion (maintenance), max initial infusion rate of 1,000 units/hr, titrate to goal aPTT

Monitoring

Activated partial thromboplastin time (aPTT)

- Collect 6 hours after initiation or rate change of heparin infusion, adjust per protocol

Goal aPTT range changes annually based on the site specific reagent used to perform the test. This is done at UK by correlating aPTT values with therapeutic heparin levels (measured by factor Xa inhibition).

Adult Full-Dose Heparin Protocol (Effective June 2007-February 2008)

Laboratory:
1. Baseline CBC, then daily while on heparin
2. Baseline PT with INR and aPTT prior to initiation of heparin
3. aPTT q6h and adjust according to sliding scale below. May decrease to daily aPTT once two consecutive aPTTs are within the therapeutic range.

Heparin Bolus and Infusion:
4. Bolus: 80 units/kg (max of 8,000 units)
5. Infusion: 18 units/kg/hour (initial max of 1,800 units/hour)
6. Discontinue all other orders for heparin products (i.e. heparin, enoxaparin)

Heparin Sliding Scale:
7. aPTT in 6 hours
8. Adjust heparin drip as follows:

Goal aPTT: 59-83 seconds

aPTT	Bolus	Hold Infusion	Rate Change	Repeat aPTT
<30	60 units/kg	0 min	increase by 3 units/kg/hr	6 hours
30-58	30 units/kg	0 min	increase by 2 units/kg/hr	6 hours
59-83	No bolus	0 min	No Change	6 hours*
84-110	No bolus	0 min	decrease by 2 units/kg/hr	6 hours
>110	No bolus	60 min	decrease by 3 units/kg/hr	6 hours

* Once two consecutive aPTTs are within range, may collect daily with AM labs

9. Round all bolus doses to the nearest 500 units, and infusion rates to the nearest 50 units/hr (1 ml/hr)

Overlapping with Oral Anticoagulation:
Oral anticoagulation (e.g. warfarin) should typically be started on Day 1 of enoxaparin or heparin treatment and should be continued along with warfarin for a minimum of four days and until INR in within desired therapeutic range on 2 consecutive occasions at least 24 hours apart.

ACS/MI Heparin Protocol (Effective June 2007- February 2008)

Laboratory:
1. Baseline CBC, then daily while on heparin
2. Baseline PT with INR and aPTT prior to initiation of heparin
3. aPTT q6h and adjust according to sliding scale below. May decrease to daily aPTT once two consecutive aPTTs are within the therapeutic range.

Heparin Bolus and Infusion: (also see chart on the right)
4. Bolus: 60 units/kg (max of 5,000 units)
5. Infusion: 12 units/kg/hour (initial max of 1,000 units/hour)
6. Discontinue all other orders for heparin products (i.e. heparin, enoxaparin)

Heparin Sliding Scale:
7. aPTT in 6 hours
8. Adjust heparin drip as follows:

Goal aPTT: 50-70 seconds

aPTT	Bolus	Hold Infusion	Rate Change	Repeat aPTT
<30	60 units/kg	0 min	increase by 3 units/kg/hr	6 hours
30-49	30 units/kg	0 min	increase by 2 units/kg/hr	6 hours
50-70	No bolus	0 min	No Change	6 hours*
71-95	No bolus	0 min	decrease by 1 units/kg/hr	6 hours
>95	No bolus	60 min	decrease by 2 units/kg/hr	6 hours

* Once two consecutive aPTTs are within range, may collect daily with AM labs

9. Round all bolus doses to the nearest 500 units, and infusion rates to the nearest 50 units/hr (1 ml/hr)

Heparin Reversal Recommendations

Protamine

- Binds to heparin forming a stable complex devoid of anticoagulant activity.
- Reserved for patients with clinically significant bleeding episodes while receiving heparin therapy. The drug is not indicated in cases of minor bleeding as withdrawal of heparin will generally result in correction of bleeding within several hours.
- Use with supportive care of the patient and possible transfusion therapy.
- Dosing
    - 1 mg of protamine will reverse approximately 100 units of heparin
    - Initial doses rarely exceed 50mg
- Infusion related adverse effects including hypotension and bradycardia can be minimized by extending the infusion time (10 minutes)
- Follow-up aPTT should be drawn 15 min post-dose to assess response

Enoxaparin

Mecahnism of Action

- Low molecular weight heparin (LMWH) derived from porcine heparin with an average molecular weight of 4500 daltons.
- Both heparin and LMWH binds to and causes a conformational change in anti-thrombin III thereby accelerating inactivation of activated clotting factors. Due to its smaller size, enoxaparin preferentially inhibits factor Xa, with an anti-Xa:anti-IIa ratio of 3.6:1.

Pharmacokinetics

Absorption (SQ)
- 90% absorbed by subcutaneous route
- Peak anti-factor Xa activity 3-5 hours after injection

Distribution
- Similar to intravascular volume

Elimination
- Primarily renal, follows linear, first order kinetics

Half-Life (based on anti-factor Xa activity)
- 6 hours (multiple doses)
- Prolonged in patients with renal insufficiency due to decreased clearance

Prophylaxis Dosing

40 mg SQ daily
- General Surgery / Medicine patients
- Orthopedic hip replacement

30 mg SQ bid
- Orthopedic Trauma patients
- Orthopedic knee replacement

Treatment Dosing

1 mg/kg SQ bid (Actual body weight)
- DVT/PE treatment
- Unstable angina and NSTEMI
- Bridge therapy to warfarin

1.5 mg/kg SQ daily
- DVT/PE treatment
    - 1mg/kg SQ bid preferred in following patients
        - Proximal DVT
        - Obesity
        - Hypercoagulable state
        - Increased bleeding risk

Monitoring

Not generally necessary
- May be considered in special populations. Those at extremes of body weight or with renal insufficiency (defined as Clcr < 30 ml/min).
- Limited data are available that correlate a specific anti-factor Xa range to antithrombotic activity or bleeding risk. Appropriate surrogate marker of antithrombotic effect when the clinical situation dictates monitoring.

Anti-factor Xa levels (LMWH level)

- Concentrations measured by the anticoag lab on Mondays, Wednesdays, and Fridays
- Collect peak concentration 3-5 hours after the subcutaneous dose
- Enoxaparin should be at steady state to account for accumulation, typically prior to third dose
- Therapeutic Range (peak concentration):
    - 0.6-1 Unit/ml (1mg/kg dosing)

Dosage adjustment

- Changes in dose can be calculated by using a ratio of dose and anti-factor Xa level
    - Assumes current Xa level is at steady state
    - Goal Xa level for treatment doses in therapeutic range

$$\text{New Dose} = \frac{(\text{Current Dose}) \cdot (\text{Goal anti-factor Xa level})}{\text{Current anti-factor Xa level}}$$

Renal Insufficiency

- ✓ Enoxaparin is primarily eliminated renally. Its use in patients with severe renal dysfunction will prolong the elimination half-life and may increase bleeding risk.
- ✓ Inverse correlation exists between Clcr and anti-factor Xa levels. Patients with severe renal impairment (Clcr < 30 ml/min) require dosage adjustment due to reduced clearance.
    - Prophylaxis dosing: Enoxaparin 30mg SQ daily
    - Treatment dosing: Enoxaparin 1mg/kg SQ daily
- ✓ UFH is recommended for dialysis patients or patients with renal insufficiency at high risk of bleeding.

Extremes of Body Weight

Underweight (<45 kg): Consider monitoring anti-factor Xa levels
Obesity: No dosage adjustment is necessary in patients with a BMI < 40 kg/m2. Data on the use and monitoring of enoxaparin in patients >150 kg is limited.

- Peak concentrations may be delayed in this population (4-6 hours)
- When compared to non-obese patients, overall exposure at steady state was 16% higher in obese population receiving the same weight-based dose (1.5mg/kg daily). Use with caution in patients > 150kg
- Consider treatment with UFH in these patients
- If LMWH used, consider dose adjustment with anti-factor Xa monitoring

Enoxaparin Reversal Recommendations

No accepted method available to neutralize enoxaparin
Protamine

- Reverses the antithrombin activity of enoxaparin but only about 60% of the anti-Xa activity.
- Reserved for patients with clinically significant bleeding episodes while receiving enoxaparin therapy. Reversal may be incomplete due to lack of anti-factor Xa neutralization. Use with supportive care of the patient and possible transfusion therapy.
- Dosing (within 8 hours of SQ dose)
    - 1 mg of protamine will reverse approximately 100 anti-factor Xa units (1 mg of enoxaparin = 100 anti-factor Xa units).
    - Repeat dose of protamine 0.5 mg per 100 anti-factor Xa units may be given if bleeding continues.

Adult Heparin Induced Thrombocytopenia (HIT) Guidelines

HIT should be considered in patients exhibiting a decrease in platelet count after 5 days of receiving a heparin/LMWH product (may be seen much sooner if previous exposure to heparin), and one of the following:

- Platelet count of less than 100000/µL OR 50% drop in baseline platelet count
- Development of a new arterial or venous thrombus
- Inflammation or necrosis at heparin injection site
- Patient with previous documented HIT or heparin induced thrombocytopenia thrombotic syndrome (HITTS) requiring treatment

Initial Assessment and labs:

- Discontinue all heparin/LMWH products (IV, SC, flushes, and coated catheters
- Collect HIT assay (ELISA)
  - Positive – initiate/continue direct thrombin inhibitor (DTI)
    - Consider venous doppler imaging to assess for potential sub-clinical DVT
  - Equivalent – initiate/continue DTI, repeat assay in 1-2 days
  - Negative – consider other causes for thrombocytopenia, discontinue DTI
- Collect baseline CMP (renal and hepatic function) and CBC
- Collect baseline aPTT, INR/PT
- Initiate treatment for suspected HIT/HITTS

The "4 Ts" Estimation of pretest probability of heparin-induced thrombocytopenia

	Points*		
	2	**1**	**0**
Thrombocytopenia	> 50% platelet fall to nadir >20	30-50% platelet fall, or nadir 10-19	<30% platelet fall, or nadir <10
Timing of onset of platelet fall	Days 5-10, or < 1 day with recent heparin (past 30 days)	> 10 days or timing unclear, or < 1 day with recent heparin (past 31-100 days)	< Day 4 (no recent heparin)
Thrombosis	Proven new thrombosis, skin necrosis, or acute systemic reaction after IV UFH bolus	Progressive or recurrent thrombosis, erythematous skin leasions, suspected thrombosis (unproven)	None
Other causes of platelet fall	None evident	Possible	Definite

- pretest probability scores: 6-8 indicates high; 4-5 intermediate; and 0-3 low.

Warkentin TE, Heddle NM. Laboratory Diagnosis of Immune Heparin-induced Thrombocytopenia. Curr Hematol Rep; 2003, 2:148-157.

Initial treatment for HIT/HITTS:

UKCMC Preferred agent based on indication

	Argatroban	Bivalirudin	Fondiparinux*
HIT / HITTS	**X**	**X**	
HIT w/ hepatic insufficiency		**X**	
HIT w/ renal insufficiency	**X**		
HIT and PCI		**X**	
HIT and CABG		**X**	
HIT and VTE prophylaxis			**X**

*Fondaparinux available for treatment of HIT through hem/onc consultation

Warfarin is not indicated as initial therapy and should be withheld until platelet count resolves.

Lepirudin (Refludan®) is available for catheter instillation in patients with a diagnosis of HIT that require an anticoagulant to maintain port patency. Concentration used is 1mg/ml. Volume dispensed should equal the size of the port.

Direct Thrombin Inhibitors (DTI):

- **Argatroban** continuous IV infusion, initial rate of 2 mcg/kg/min
  - Requires dosage adjustment in patients with hepatic insufficiency, (Child-Pugh score >6) initial dose 0.5 mcg/kg/min

OR

- **Bivalirudin** continuous IV infusion, initial rate of 0.2 mg/kg/hr
  - Requires dosage adjustment in patients with renal insufficiency (Clcr < 30 ml/min), initial bolus of 0.1 mg/kg, continuous infusion of 0.1 mg/kg/hr

OR

Factor Xa Inhibitor (hematology/oncology consultation required):

- **Fondaparinux** (Arixtra®), weight based dosing (actual body weight)
- Contraindicated in patients with a Clcr < 30 ml/min
- Assess patient for appropriateness of SC route and use of agent with long half-life
- Monitor CBC to assess platelet count and evidence of bleeding

Routine labs/monitoring (direct thrombin inhibitors):

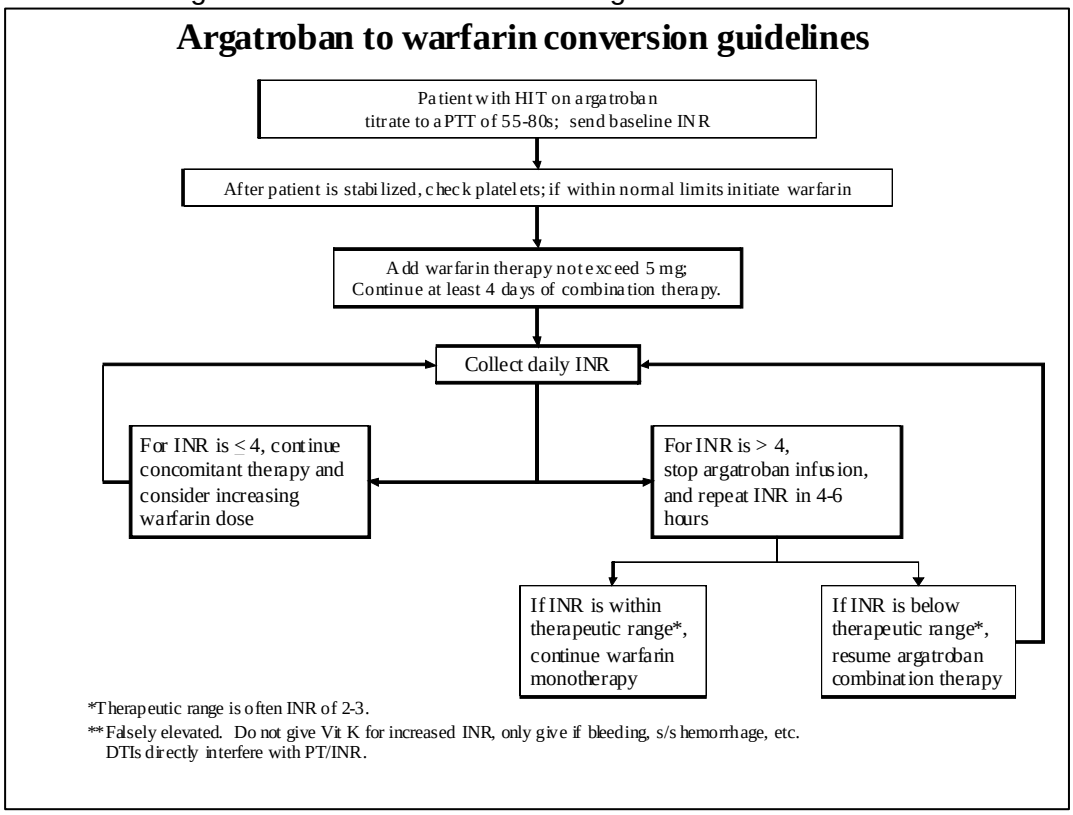
- Collect aPTT 2 hours after initiation of therapy
- Adjust direct thrombin inhibitor (DTI) dose according to nomogram to achieve a goal aPTT of 55-80 seconds (1.5-3x baseline)
- Collect aPTT 2 hours after change in infusion rate
- After 2 consecutive aPTTs in the therapeutic range, collect aPTT daily for the remainder of therapy
- Monitor CBC daily to assess platelet count and evidence of bleeding

Argatroban nomogram for management of HIT Initiate rate of 2 mcg/kg/min (normal hepatic function)	
aPTT	**Dosage Adjustment**
<30	increase by 1 mcg/kg/min
30-54	increase by 0.5 mcg/kg/min
55-80	No Change
81-100	decrease by 0.5 mcg/kg/min
>100	Hold for 30 min, decrease by 1 mcg/kg/min

Bivalirudin nomogram for management of HIT Initial rate 0.2-0.25 mg/kg/hr	
aPTT	**Dosage Adjustment**
<30	increase by 0.1 mg/kg/hr
30-54	increase by 0.05 mg/kg/hr
55-80	No Change
81-100	decrease by 0.05 mg/kg/hr
>100	Hold for 30 min, decrease by 0.1 mg/kg/hr

Initiation of warfarin:

- Should be held until platelet count returns to above 100000/µL
- Combined therapy of a DTI with warfarin should be continued for a minimum of 4 days and until the INR is in the desired range
- Argatroban can cause an elevation in INR beyond that seen with warfarin alone (reversal with vitamin K not necessary)
  - Collect baseline INR on argatroban prior to initiation of warfarin
  - Refer to argatroban to warfarin conversion guidelines



Patients with HIT/HITTS Undergoing Percutaneous Coronary Intervention (PCI)

Bivalirudin Dosing

- Patient currently on infusion of bivalirudin
  - Initial bolus of bivalirudin 0.5 mg/kg, increase infusion rate to 1.75 mg/kg/hr
- Patient not currently on infusion of bivalirudin
  - Initial bolus of bivalirudin 0.75 mg/kg, initiate infusion rate of 1.75 mg/kg/hr
- Check activated clotting time (ACT) 5 minutes after bolus
  - If less than 225s, give additional 0.3 mg/kg bolus
- Continue infusion for up to 4 hours post-procedure
- If additional anticoagulation is necessary for bridging to warfarin or other indication, continue at a rate of 0.2 mg/kg/hr
  - Adjust according to nomogram to achieve goal aPTT of 55-80s

Patients with HIT/HITTS Undergoing On-Pump Coronary Artery Bypass Surgery

Bivalirudin:

- 1 mg/kg IV bolus, followed by 2.5 mg/kg/hr infusion for the duration of the procedure
  - In addition, bivalirudin 50 mg is added to the pump prime
  - Discontinue infusion 15 min prior to expected separation from CPB
- Goal to maintain ACT > 2.5-times baseline
  - Administer additional 0.1-0.5 mg/kg boluses if subtherapeutic

Patients with HIT/HITTS Undergoing Off-Pump Coronary Artery Bypass Surgery (OPCAB)

Bivalirudin:

- 0.75 mg/kg IV bolus, starting dose of 1.75 mg/kg/hr infusion for the duration of the procedure
- Goal to maintain ACT above 300 seconds
- Adjust infusion rate by 0.25 mg/kg/hr increments to maintain ACT within desired range

Patients required VTE prophylaxis with history of HIT or patients with resolved HIT/HITTS:

Factor Xa Inhibitor:

- Fondaparinux 2.5 mg SC daily
- Monitor CBC daily to assess platelet count and evidence of bleeding