Basic Pharmacokinetic Principles
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I. General principles

Applied pharmacokinetics - the process of using drug concentrations, pharmaco-kinetic principles, and pharmacodynamic criteria to optimize drug therapy in individual patients.

Goals: - optimization of drug therapy for individual patients
- increase probability of desired effect
- reduce toxicity without compromising efficacy
- increase efficacy without unacceptable toxicity

A. Rationale

Drugs whose toxicities may manifest at dosages close to those recommended for therapeutic effect (i.e.- a narrow therapeutic index) are candidates for therapeutic drug monitoring (TDM). Usually, drugs with high toxic:therapeutic concentration ratios (penicillin, cephalosporins, benzodiazepines, etc.) are not monitored. Inter- and intrapatient variability in elimination, metabolism, etc. may also be a reason to monitor drug concentrations and adjust for the desired endpoint. Reasons to do TDM other than for efficacy and toxicity include cost minimization, decreased length of stay, improved patient outcome or improved tolerability of an agent.

B. Determinants of a dosage regimen

As seen in Figure 1, there are many factors which contribute to determining an appropriate dosage regimen for a patient. Pharmacokinetics simply facilitates the rapid achievement of an appropriate dosage regimen and serves as a useful means of evaluating existing dosage regimens.

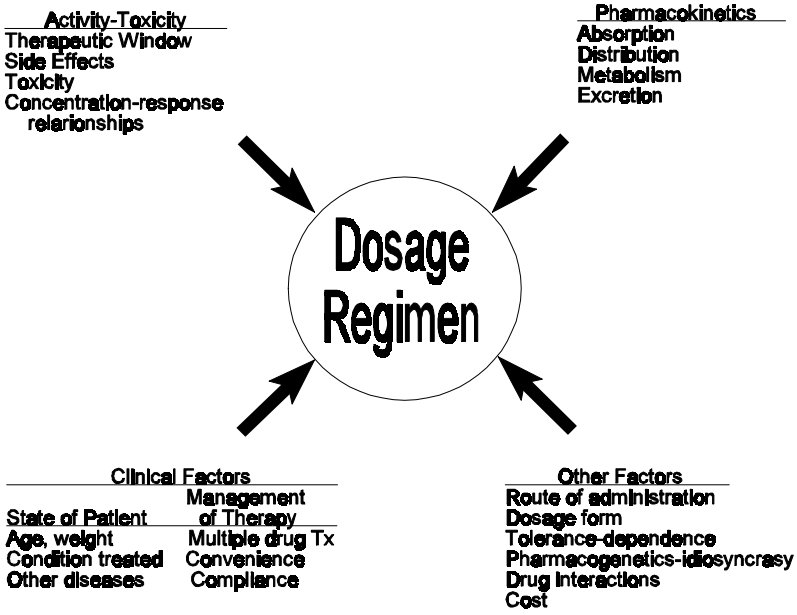


Figure 1

C. Drug which are commonly monitored:

Digoxin	Antineoplastics	Lithium
Aminoglycosides	Busulfan	Antidepressants
Antiarrythmics	Methotrexate	Anticonvulsants
Theophylline	6-MP	Antipsychotics
Vancomycin	Carboplatinum	Cyclosporine

D. Therapeutic range

1. Definition: range of drug concentrations within which the probability of the desired clinical response is relatively high and the probability of unacceptable toxicity is relatively low.

2. Misconceptions about a "therapeutic" range:

a. The therapeutic range is well-defined, well-researched and backed up by sound scientific data for each drug.
In fact, the "therapeutic" range for most drugs is based on anecdotal data on efficacy or, more likely, lack of observed toxicity at the concentrations reported.

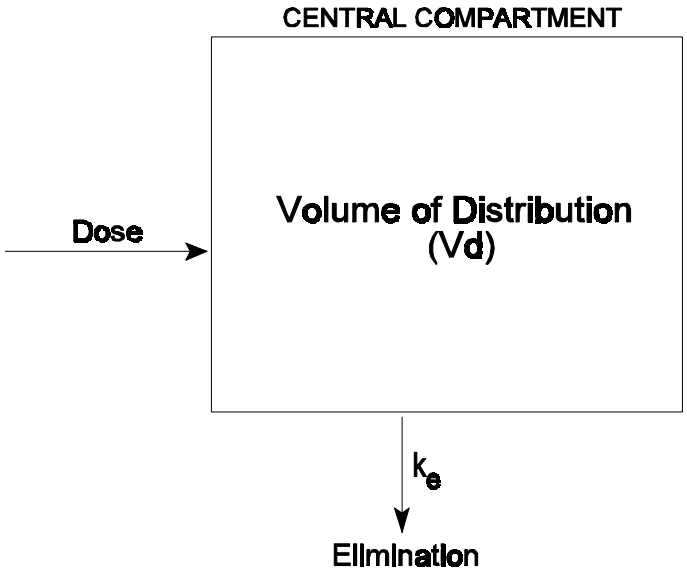
b. Drug concentrations in the therapeutic range result in the desired clinical response.
The reported ranges for most drugs are merely guidelines which allow the clinician to target a concentration to avoid toxicity and increase the probability of seeing a desired pharmacodynamic response. Although most individuals experience favorable effects with serum concentrations in the therapeutic range, there is much interpatient variability in the effect of a given drug concentration. Patients may show signs of toxicity or lack of response even when drug concentrations are "therapeutic." Each patient is an individual who requires adjustments of drug dosages based observed clinical response. Always treat the patient, not the number.

II. Compartment Models

Compartment modeling is a means to describe the physiologic distribution of a drug in a biologic system after administration (oral, IV, IM, etc). For clinical use, a one-compartment model is often sufficient, although a two compartment model or Michaelis-Menten model may be required.

A. **One-compartment model** (Fig. 5) assumes drug distributes uniformly, instantaneously, and homogeneously throughout the compartment (volume of distribution) and that elimination begins immediately after infusion. Assumes the body is a single large compartment.

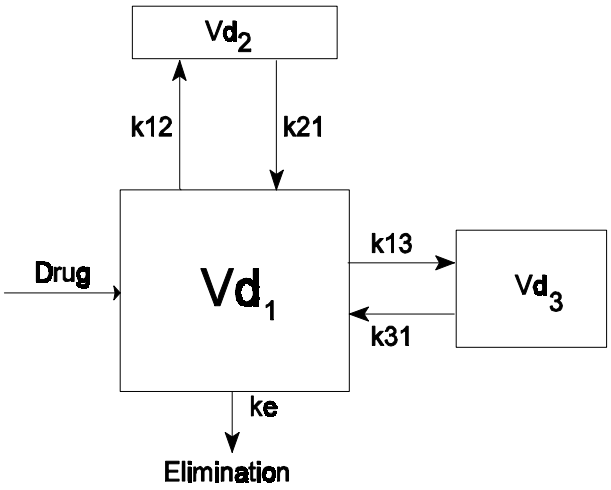
Figure 2



B. **Multi-compartment model** - drug distributes into more than one compatment. The rate and extent of distribution between compartments differs (Fig 3). For example, the distribution into the plasma may be

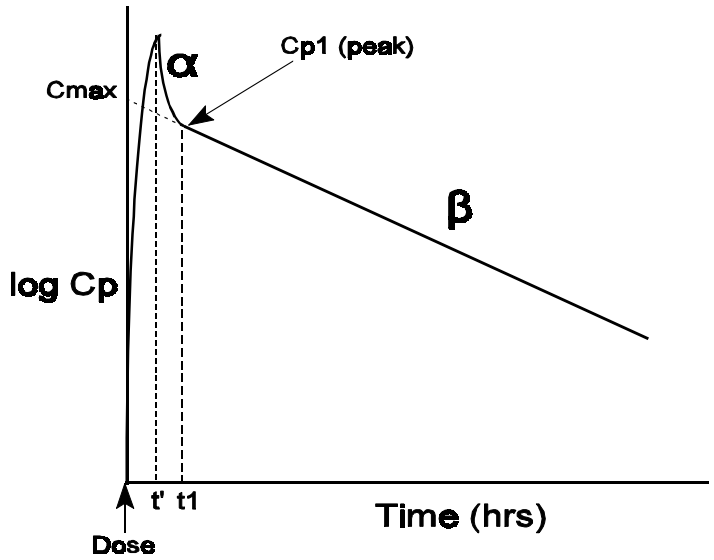
different from the distribution into pulmonary tissue (aminoglycosides), heart muscle (digoxin), CSF and brain (Vancomycin, cephalosporins, etc).

Figure 3



C. Application
to pharmacokinetic sampling - In reality, most all drugs have some initial distribution from the administration compartment. If the "therapeutic" concentration or target organ is not in this initial compartment, then this time frame must be avoided when sampling drug concentrations. e.g.- aminoglycosides are sampled 30 minutes after a 30 minute infusion to avoid drawing the sample during the initial distribution phase and having a falsely elevated "peak" concentration. In another example, digoxin concentrations are drawn at least 6 hours after an oral dose because the distribution into the site of action (heart) takes longer than distribution into the blood compartment.

Figure 4



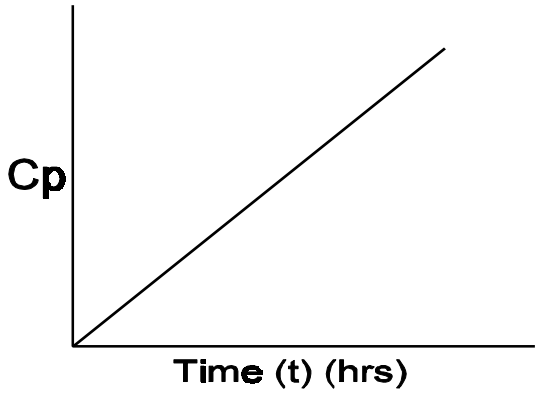
" - initial distribution phase after IV bolus administration
$ - terminal elimination phase or elimination from the central compartment
Peak - concentration drawn at end of initial distributive phase
Cmax- concentration that occurs immediately after administration.
Cmax ... Peak - if half-life is short relative to the end of infusion and "peak" sample (gent/tobra).
t1 - time from end of infusion to Cp1
t' - duration of infusion (hrs)

III. First Order versus Zero Order Administration and Elimination

A. First Order (Linear) Kinetics:
1. Administration - serum concentrations (Cp) change proportionately with a change in dose.

e.g. - dose increase from 40mg to 80mg doubles the Cp.

Figure 5



2. Elimination - rate of elimination is proportional to the amount of drug in the body at that time. i.e. - the amount of drug removed per unit time (elimination rate) is a constant percentage of the total drug remaining in the body.

Figure 6

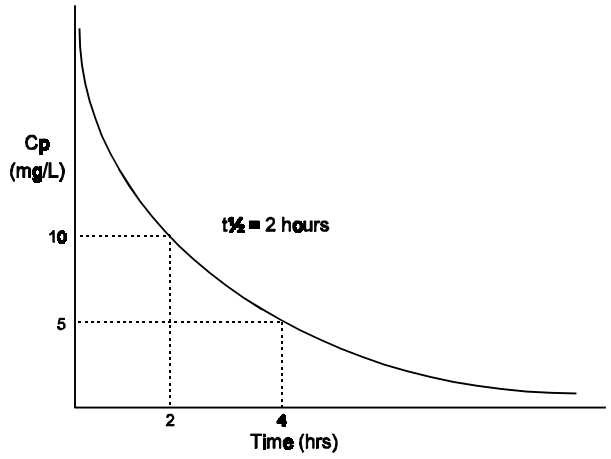
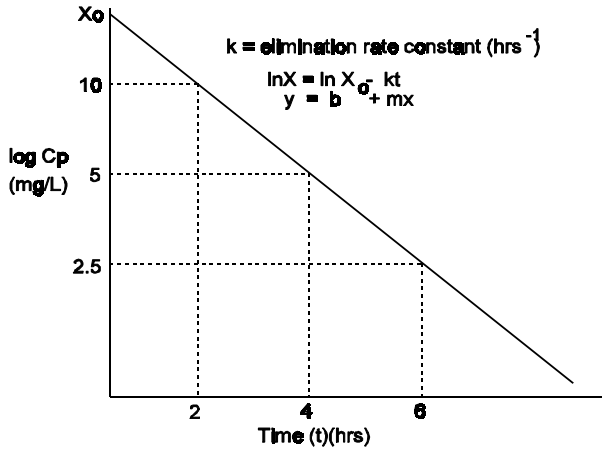


Figure 7



Figures 6 and 7 represent a drug eliminated in a linear (first-order) manner. When plotted on log-linear paper, the elimination curve becomes a straight line which allows us to calculate a slope (elimination rate) for that drug. Assumptions in first-order kinetics is that clearance (Cl) and the volume of distribution (Vd) remain constant.

B. Non-linear / Michaelis-Menten / Saturable / Capacity-limited metabolism
Examples: phenytoin, salicylates, theophylline (high dose), ethanol

1. Increased dose results in a disproportionate increase in Cp (Fig.8)
2. Non-linearity may be the result of saturation of binding sites, saturation of clearance mechanisms, or active transport or other absorption mechanism.
3. Clearance and half-life (t½) may vary with the change in Cp (Cl may decrease as Cp increaes).

Figure 8

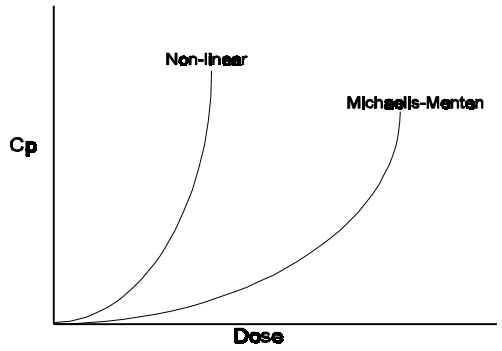
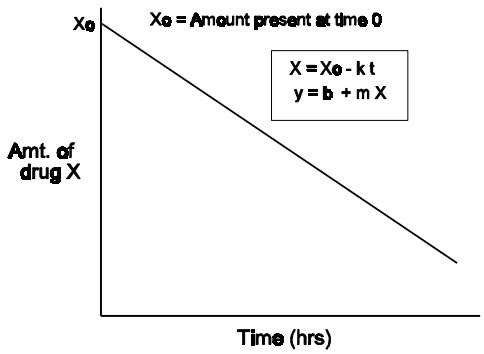


Figure 9



III. Calculations and other fun stuff

A. Creatinine clearance (Clcr) - a useful estimation of a person's glomerular filtration rate

Adults:

Children/neonates 1-18 years (mL/min/1.73m^2):

k = proportionality constant
L= height (cm)
Scr = serum creatinine (mg/dL)

Crockroft-Gault: $Clcr = \frac{(140 - age)(kg)}{(Scr)(72)}$ (X 0.85 for females)

k
values: LBW during 1st year of life = 0.33
Term AGA during 1st year = 0.45
Children and adolescent girls = 0.55
Adolescent boys = 0.70

$$CrCl = \frac{k\ (L)}{Scr}$$

Normal Values:

Age				GFR (mean)
Newborns (<24hr)	1.07	±	0.12	mL/min/kg
Premature (>24hr)	No ref. values			
5-7 days	50.6	±	5.8	mL/min/1.73m^2
1-2 months	64.6	±	5.8	mL/min/1.73m^2
3-4 months	85.8	±	4.8	mL/min/1.73m^2
5-8 months	87.7	±	11.9	mL/min/1.73m^2

9-12 months	86.9	±	8.4	mL/min/1.73m^2
1½ years to Adolescence				
Males	124	±	25.8	mL/min/1.73m^2
Females	108.8	±	13.5	mL/min/1.73m^2
Adults (post-pubertal)				
Males	105.0	±	13.9	mL/min/1.73m^2
Females	95.4	±	8.0	mL/min/1.73m^2

B. Volume of Distribution (Vd) - hypothetical volume of body fluid through which drug must have distributed to produce a specific serum level.

or

- the size of a compartment necessary to account for the total amount of drug in the body if it were present throughout the body at the same concentration found in the plasma.

1. Major factors affecting Vd:

   a. **Lipid** versus **water** solubility characteristics of the drug

      Lipid vs H_20 solubility - drugs which have a high water solubility and low lipid solubility (amino-glycosides) will have a small Vd because they are mainly confined to the intravascular space and may approximate its total volume (the smallest Vd possible is one equal to the intravascular volume). Conversely, drugs that are more lipid soluble (digoxin) will have a larger Vd because they can move out of the central (plasma) compartment and have greater tissue distribution.

   b. **Plasma** versus **tissue** protein binding of the drug

      Plasma vs Tissue binding - as you might expect, drugs which are largely bound to plasma proteins (e.g. - furosemide, etc) will remain in the plasma compartment and have a small Vd. In reality, most drugs exhibit a combination of these factors accounting for a wide variety of Vd's.

2. Being able to conceptualize the basic concepts of Vd, however, can help one predict physiologic factors that may alter a drug's distribution during therapy. Changes in plasma protiens (9 albumin, 8 "-1-acid glycoprotein) or body water (dehydration, volume overload, etc.) may affect the measured concentrations or pharmacodynamic effects of some agents.

   Neonates and children have a larger percent total body water (TBW) compared to adults. This means the estimated Vd for drugs with a small Vd (AG's) will be larger in this population.

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3. Since the Vd accounts for all of the drug in the body, it can be used to estimate the loading dose needed to achieve a desired Cp (plasma concentration)

$$LD = \frac{(Vd)(Cp_{desired})}{(S)(F)}$$

where: LD (mg/kg) = amount of drug needed
Vd (L/kg) = estimated Vd based on population parameters
$Cp_{desired}$ (mg/L) = desired target concentration
S = salt form
F =bioavailability = 1 because its given I.V.

When there is already drug on board, the following equation can be used:

$$LD = \frac{(Vd)(Cp_{desired} - Cp_{obs})}{(S)(F)}$$

Example: Ima Wheezer's theophylline Cp = 8 mg/L and you want it to be 12 mg/L.. Vd . 0.5 L/kg. Wt=30 kg. How much aminophylline would you need to give I.V. to accomplish this?

LD=2.5 mg/kg or a total of 75 mg of aminophylline
S = 0.8 because aminophylline is 80% theophylline
F = 1 because its given I.V.

4. If the Cpmax is measured off the first dose (no drug on board) and accurate determination of the Vd can be calculated:

$$Vd = \frac{(S)(F)(Dose\ (mg))}{Cp\ (mg/L)}$$

$$LD = \frac{(0.5\ L/kg \times 30\ kg)\ (12\ mg/L - 8\ mg/L)}{(0.8)(1)}$$

If not after the first dose, the change in the Cp will reflect the Vd:

$$Vd\ (L/kg) = \frac{(S)(F)(Dose\ (mg/kg))}{(Cpmax\ (mg/L)) - (Cpmin\ (mg/L))}$$

C. Clearance (Cl) - the intrinsic ability of the body to remove drug from the blood or plasma. [note: the word **plasma** is used instead of serum since most drugs are assayed in plasma. Serum is simply blood which was allowed to clot before spinning (clotting factors removed) i.e.- blood is collected in a non-heparinized tube, allowed to clot, then centrifuged and the serum is assayed. Physiologically, plasma (or blood) is the appropriate term to use when discussing clearance.]

- clearance is not representative of the amount of **drug** removed from the body. Instead, it is the amount of **blood** (plasma) that is cleared of the drug per unit time. The amount of drug removed depends on both Cp and Cl. Cl can be thought of as the proportionality constant that makes the average steady-state plasma concentration ($Cpss_{ave}$) equal to the rate of administration.

a. At steady-state (ss), rate in = rate out

Rate out (mg/hr)= Cl (L/hr) X Cp (mg/L) therefore,

Rate in (mg/hr) = Cl (L/hr) X Cpss (mg/L)

b. If a drug is given by continuous infusion (aminophylline), Cl can be calculated from the Cpss:

$$Cl(L/hr) = \frac{(S)(F)(Dose(mg/hr))}{Cpss(mg/L)} = \frac{(S)(F)(Dose/T)}{Cpss_{ave}(mg/L)}$$

Therefore, to calculate a maintenance dose,

$$MD = \frac{(Cl)(Cpss_{ave})(T)}{(S)(F)}$$

But, Clearance is not so simple....
$Cl_{total} = Cl_{hepatic} + Cl_{renal} + Cl_{other}$

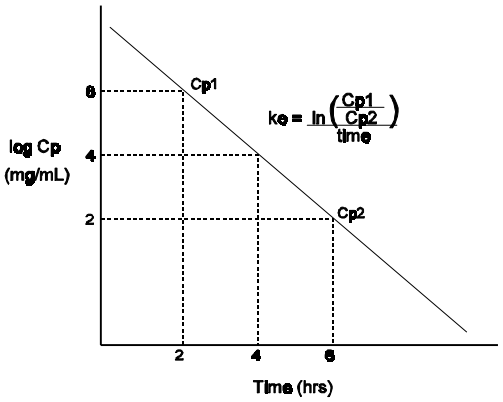
Average Clearance Values

Drug	$Cl_{hepatic}$	Cl_{renal}	Cl_{total}
Digoxin	30%	70%	1.7 mL/min/kg
Quinidine	82%	18%	4.7 mL/min/kg
Aminoglycosides	----	>90%	1 mL/min/kg
Theophylline	>90%	----	0.7 mL/min/kg

D. Elimination rate constant (Ke or k) - represents the percent of drug eliminated per unit time. It can be calculated using any two plasma concentrations measured during the elimination phase ($) drawn at least one half-life apart.

where: t = change in time (hrs) from Cp_1 to Cp_2

Figure 10



$$Ke = \frac{\ln(\frac{8}{2})}{4} = .347\ hrs^{-1}$$

$$= \frac{0.693\ (Vd)}{Cl}$$

E. Half-life (t½) - time necessary for the Cp to decrease 50%

$$t_{1/2} = \frac{0.693}{ke\ (hrs^{-1})}$$

, As a rule of thumb, it takes approximately 5 t½'s to reach steady-state. But, realistically, waiting 3-4

t½'s is appropriate if you remember the Cp will still increase somewhat.

# t½'s	% Steady-state
1	50
2	75
3	87.5
4	93.75
5	96.875

, For drugs with a short half-life (t½<<I) such as aminoglycosides, 3-4 t½'s can occur within a single dosing interval. However, this does not represent steady-state; in this case you must wait 3-4 **doses** before steady-state will occur.

IV. Equations: Bolus vs. Intermittent Infusion

A Bolus Model - where the elimination during the infusion is small compared to the total dose. i.e. - drugs with long half-lives or where the dosing interval is much shorter than the half-life such as phenobarbital, theophylline (rapid release,intermittent IV administration), aminoglycosides (if t½>3 hrs), vancomycin (if t½> 6 hrs).

Figure 11

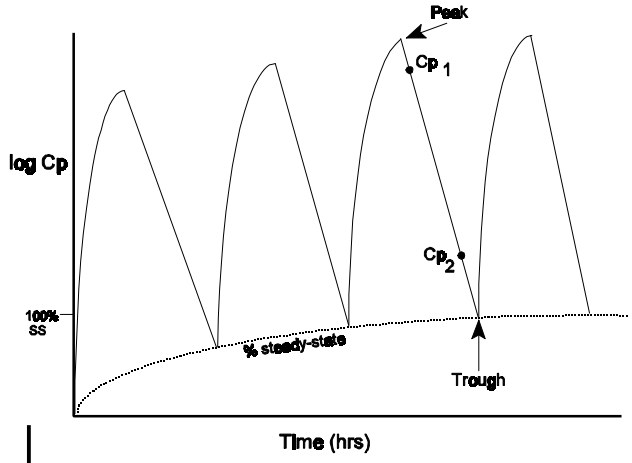
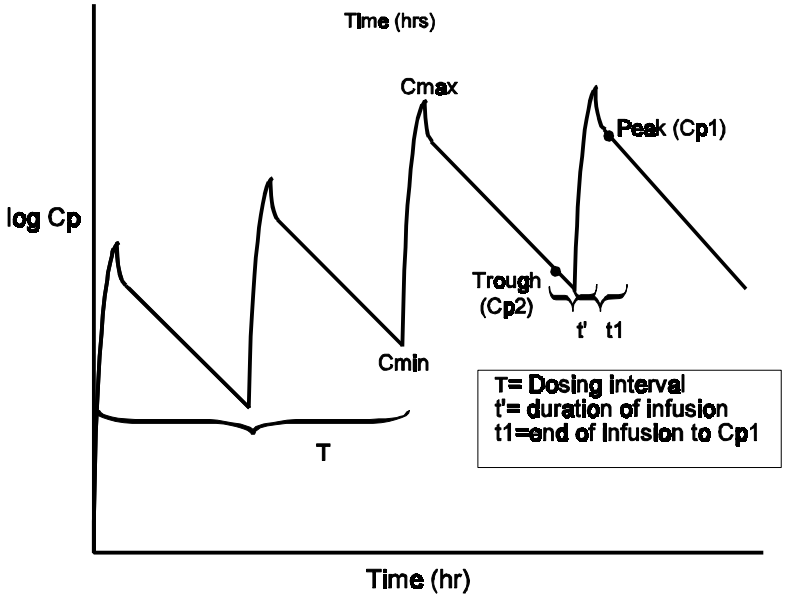


Figure 12



Benzodiazepine Pharmacokinetic vs Pharmacodynamic Considerations

Benzodiazepine Pharmacokinetics							
Drug	t½ " (min)	t½$ (hr)	Vd (L/kg)	Cl (mL/min/kg)	Protein Binding	Clinical Effect (hr)	Active Metaboltes (t½)
Diazepam	30-60	20-50	0.7-1.7	0.2-0.5	97-99	0.25-1	Desmethydiazepam (30-200) 3-Hydroxydiazepam (5-20) Oxazepam (3-21)
Midazolam	6-15	1.7-2.6	1.1-1.7	6.4-11	97	2	1-hydroxymethyl midazolam (1-1.3)
Lorazepam	2-7	4-22	0.8-1.3	0.8-1.2	96	12-24	none (glucuronidated)

Midazolam

Water-soluble salts depend on pH

pH <4 - water soluble (as in parenteral formulations - no propylene glycol needed)
pH >4 - lipid soluble (physiologic pH - increases absorption and distribution to CNS)

Pharmacokinetics in children

Vd: 1.3 L/kg (significantly increases with obesity)
t½: 1.2 hrs
Pharmacodynamic effects • Cp

g Lipophilicity relates to large Vd, but rapid t½$ accounts for short duration of action and less accumulation than lorazepam

Lorazepam

Very lipid soluble with rapid distribution to fatty tissues
t½$: much slower than midazolam

g duration of clinical effect increases with successive dosing due to accumulation