DRUG USE IN PATIENTS WITH RENAL DISEASE

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MEDICAL GRAND ROUNDS
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RENAL CONTRIBUTION TO HANDLING OF DRUGS

I. INTRODUCTION

Renal dysfunction importantly influences the handling of an impressive number of drugs:

ANESTHETICS
Alcuronium
Gallamine
Metocurine
Pancuronium
D-tubocurarine

ANTIANXIETY AGENTS-SEDATIVES-HYPNOTICS
Barbital

ANTICOAGULANTS-ANTIFIBRINOLYTICS
Epsilon amino caproic acid

ANTIHISTAMINES
Cimetidine

ANTIMICROBIALS
Aminoglycosides--all
Cephalosporins--all except cefoperazone
Lincomycin
Moxalactam
Penicillins--all except nafcillin, cloxacillin, dicloxacillin and oxacillin
Polymyxins B and E (colistin)
Spectinomycin
Sulfonamides--all
Tetracyclines--all except chlortetracycline, doxycycline, and minocycline
Thiamphenicol
Trimethoprim
Vancomycin

ANTIMETABOLITES-ANTINEOPLASTICS
Bleomycin
Cis-Platinum
Cytarabine
Methotrexate

ANALGETICS
Meperidine (pethidine)
Propoxyphene

ANTI-INFLAMMATORY AGENTS
Azopropazone

ANTICHOLINERGICS-CHOLINERGICS
Metoclopramide
Neostigmine
Pyridostigmine

ANTIMANICS
Lithium

ANTIFUNGALS
Flucytosine
Miconazole

ANTIMALARIALS
Chloroquine

ANTITUBURCULAR AGENTS
Para-aminosalicyclic acid
Cycloserine
Ethambutol
Isoniazid
Terizidone

ANTIVIRAL AGENTS
Amantadine
Vidarabine

ANTISPASTICITY AGENTS
Baclofen

BRONCHODILATORS
Dyphylline

HYPOGLYCEMICS
Acetohexamide
Chloropropamide
Glisoxepide

HYPOURICEMIC AGENTS
Allopurinol

MISCELLANEOUS
Clodronate

CARDIOVASCULAR AGENTS
Antiarrhythmics
N-acetylprocainamide
Bretylium
Disopyramide
Procainamide

Antihypertensives
Acebutolol
Atenolol
Captopril
Clonidine
Diazoxide
Methyldopa
Nadolol
Pindolol
Sotalol

Blood Lipid Lowering Agents
Clofibrate

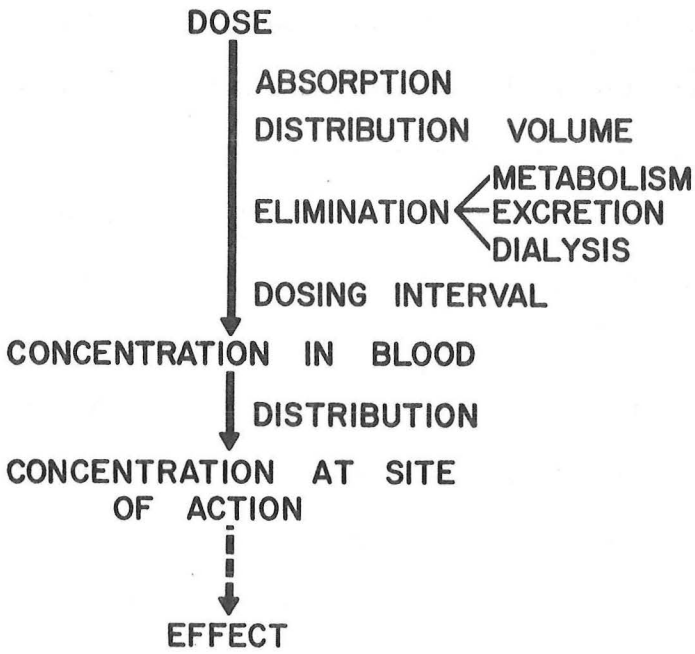
Cardiac Glycosides
Digoxin

Renal function can permute the relationship between drug dose and effect in a variety of ways. Effects on absorption, distribution volume and elimination influence the concentration of drug attained in blood. Consequently, such effects can often be detected and/or prevented by monitoring of serum concentrations of drugs. However, the relationship between the concentration of drug in serum and response may also be changed. Consequently, monitoring serum concentrations alone is insufficient for optimal therapeutics and must be accompanied by clinical monitoring of end points of efficacy and toxicity. In addition accumulation of active metabolites that are not measured by conventional assays makes interpretation of serum concentrations of some drugs particularly hazardous. Since renal function can affect drug disposition in so many different ways, the astute clinician must be aware of these

potential mechanisms to optimally call upon his clinical skills and laboratory armamentarium to best care for his patients. This section will discuss principles of the effects of renal disease on response to drugs using specific examples for illustration. This will then provide a framework for more detailed consideration of individual drugs but, more importantly, will provide a set of principles applicable to any therapeutic setting.

In simplest terms, one must consider each of the different ways in which changes in renal function can affect the relationship between the administered dose of a drug and the response to that drug. The following figure depicts a general schema by which one can subdivide the determinants of the relationship between dose and response and analyze them separately.

PHARMACOKINETIC - DYNAMIC SCHEMA



Even though the pharmacological role of the kidney can be analyzed with respect to each of the determinants indicated in the schema, one must be aware that changes of the relationship between dose and response can occur by permutations of any one or a combination of the determinants.

II. DETERMINANTS OF THE RELATIONSHIP BETWEEN THE DOSE OF A DRUG AND ITS CONCENTRATION IN BLOOD

A. Absorption

Changes in absorption can occur by affecting rate and/or extent of absorption. The rate of absorption determines the time at which the peak concentration of drug is reached in blood and its magnitude. The extent of absorption determines how much of the drug enters the system and, consequently, contributes only to the magnitude of its concentration.

The effects of renal dysfunction on gastrointestinal absorption have not been examined. However, one might speculate that uremia itself, changes in potassium homeostasis, administration of phosphate binders, etc. could affect rate and/or extent of absorption. One clear example of an effect of the kidney on absorption is the decreased intestinal absorption of calcium caused by insufficient 1-hydroxylation of 25-OH vitamin D_3 that occurs with decreased nephron mass and in renal tubular acidosis. Bianchetti, et al. reported the bioavailability of propranolol to increase in patients with renal disease presumably due to a secondary effect to decrease presystemic elimination. However, a more detailed study did not support these findings. It does appear, however, that

presystemic elimination of propoxyphene decreases in end stage renal failure resulting in greater bio-availability. It behooves the astute clinician to be cognizant of possibilities for abnormal absorption of drugs in caring for his patients.

Rate and extent of absorption from intramuscular or subcutaneous sites can also be changed by a variety of factors. For example, phenytoin and some of the benzodiazepines precipitate in muscle and, consequently, are absorbed erratically over prolonged periods of time. Patients in shock perfuse peripheral sites poorly and absorb parenterally administered drugs unpredictably. Again, while studies in patients with renal dysfunction have not been reported, acidemia, disrupted volume and electrolyte homeostasis, etc. could cause changes in absorption from intramuscular or subcutaneous sites.

B. Distribution

Effects of renal dysfunction on drug distribution will be considered in two separate parts of this discussion. This section will include effects on distribution which change the total concentration of drug (free plus protein bound) in blood and a later section will describe distribution effects in which the concentration of drug in blood remains the same but its access to its site of action changes.

It is clear that systemic pH, degree of protein binding, disease states and other diverse factors can affect the distribution of a drug into tissues:

POTENTIAL MECHANISMS OF EFFECT OF RENAL DYSFUNCTION ON DRUG DISTRIBUTION

Changes in systemic pH
- acidemia of uremia
- of renal tubular acidosis
- alkalemia of potassium depletion

Hypoalbuminemia

Displacement of drugs from protein
- by accumulated endogenous compounds
- by other drugs

Altered binding characteristics of protein

The mechanism of these effects, their consequences, and clinical relevance are poorly defined. Renal dysfunction can result in changes in systemic pH such as the acidemia of uremia or of renal tubular acidosis or the alkalemia of potassium depletion; these pH changes can affect distribution of drugs to tissues. The hypoalbuminemia of nephrotic syndrome, the displacement of protein-bound drugs by endogenous organic acids that accumulate in uremia and the altered albumin with decreased capacity to bind drugs in uremia all can affect distribtuion. Over and above these described changes in distribution that occur in renal dysfunction, renal disease per se by unknown mechanisms may affect how drugs distribute to tissues.

With the exception of digoxin, changes in distribution are important only with drugs that are highly protein-bound (approximtely 90% or more of the drug normally being bound), and with renal disease, one is only concerned with acidic drugs. A list of drugs of potential

concern would include penicillins, cephalosporins, sulfonamides, thiazide and loop diuretics, sulfonylureas, non-steroidal antiinflammatory drugs, etc., but no clinically important changes in distribution have been reported with these drugs. Quantitatively important distribution-related effects have been described with phenytoin, valproic acid, coumadin, salicylates, thiopental and diazoxide. Phenytoin, valproic acid and coumadin represent drugs in which effects on distribution cause a change in the concentration of drug in blood. With salicylates, thiopental and diazoxide changes occur in the relationship between the concentration of drug in blood and its effect. These drugs will be considered subsequently.

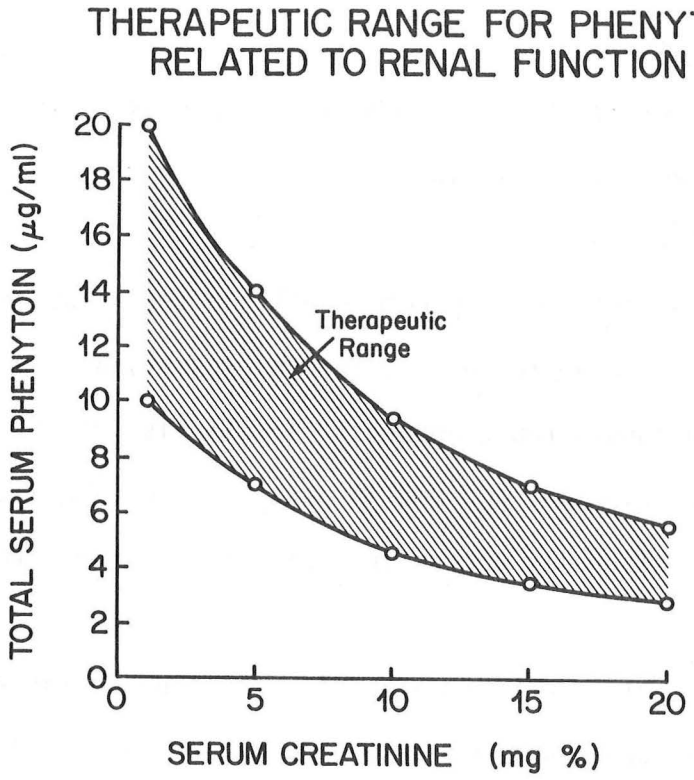
In both hypoalbuminemia and uremia, phenytoin, valproic acid and coumadin are displaced from albumin increasing the amount of drug free in plasma. This displacement from binding in itself would cause an increased pharmacologic effect since the amount of drug accessible to its site of action is related to the amount of free drug in plasma. However, this free drug is also available for elimination and for distribution into tissue in which the drug is not active. The overall result is that a steady-state is reached in which the concentration of drug free in plasma is virtually the same as in the unperturbed condition, the pharmacologic effect is the same, but the total concentration of drug in blood (that free plus that bound) is less than that before displacement. This consequence is illustrated schematically for phenytoin in the following figure:

Phenytoin in Renal Failure

Free	**1.0**		**5.5**		**1.0**
		Displacement From Protein →		**Steady State** →	
Bound	**9.0**		**4.5**		**4.5**
TOTAL	**10.0**		**10.0**		**5.5**

The clinical importance of this phenomenon is that the amount of drug administered to the patient remains the same, i.e., for phenytoin approximately 300 mg/day. The "therapeutic" concentration of phenytoin in blood in patients with the nephrotic syndrome or uremia, however, is 1/2 to 1/3 that in normals. Consequently, the importance of this effect is in interpretation of measurements of phenytoin concentrations in blood. "Low" total concentrations of phenytoin or valproic acid in a

uremic or nephrotic patient should not be misinterpreted as subtherapeutic. This interpretive problem does not occur with coumadin, for one monitors the response to the anticoagulant rather than its blood concentration. The following figure depicts the change in the "therapeutic range" for phenytoin as a function of the level of uremia:



As noted above, digoxin is the exception to the general rule regarding changes in distribution. In end-stage renal failure by unknown mechanisms, the volume of distribution of digoxin is decreased and a smaller loading dose is needed to achieve a given concentration in blood. This dose adjustment is in addition to the reduced maintenance dose of digoxin required in end-stage renal disease caused by the decreased ability of the kidney to eliminate digoxin.

C. Elimination

Drugs are eliminated by metabolism and/or excretion, or in special circumstances, by dialysis.

1. Metabolism

Metabolism occurs predominantly in the liver and the kidney's metabolic pathways for drugs, though present, are relatively inconsequential. A considerable amount of insulin is metabolized by the kidney. This observation may account in part for the decreased insulin requirement that occasionally occurs in a diabetic as renal function deteriorates.

The most important aspect of metabolism relating to the kidney is that by the liver in which metabolites of drugs are pharmacologically active and dependent on the kidney for elimination. For example, procainamide is acetylated to N-acetylprocainamide (NAPA) which is itself an anti-arrhythmic and which is eliminated by the kidney. Consequently, in renal failure NAPA accumulates preferentially to procainamide and may do so in amounts that become toxic. Interpretation of serum concentrations of procainamide in a patient with azotemia becomes difficult for

both procainamide and NAPA contribute to the pharmacologic effect while only the former is measured in many assays and "therapeutic" concentrations for the latter have not been well defined. One must emphasize the need for clinical assessment of pharmacologic effect rather than reliance on and possible misinterpretation of serum concentration measurements. Some of the oral sulfonylureas are converted to active metabolites which accumulate in uremia, potentially causing prolonged and long-lasting hypoglycemia. Meperidine (pethidine) and propoxyphene are metabolized to nor-meperidine and nor-propoxyphene which depend on the kidney for elimination. Accumulation of the metabolite can result in seizures or cardiovascular collapse, respectively. Oxypurinol, the active metabolite of allopurinol also accumulates in uremia though the clinical importance is unclear. A list of drugs with active metabolites which accumulate to a clinically important degree in patients with renal dysfunction includes:

DRUG	METABOLITE
Acebutolol	N-acetylacebutolol
Acetohexamide	Hydroxyhexamide
Allopurinol	Oxypurinol
Cefotaxime	Desacetylcefotaxime
Clofibrate	Parachlorophenoxy-isobutyric acid
Cyclophosphamide	4-Hydroxycyclophosphamide and aldophosphamide
Cytarabine	Uracil arabinoside
Digitoxin	Digoxin
Meperidine (pethidine)	Normeperidine
Methimazole	3-methyl-2-thiohydantoin
Metoprolol	α-hydroxymetoprolol
Nalidixic acid	7-hydroxynalidixic acid
Pancuronium	
Procainamide	N-acetylprocainamide
Propoxyphene	Norpropoxyphne

By uncertain mechanisms, renal disease appears in some circumstances to secondarily decrease hepatic elimination of some drugs. For drugs which can be eliminated by both the liver and the kidney, one would expect a decrease in the renal component to result in a compensatory increase in the hepatic. One cannot, however, make this assumption.

2. Excretion

Some drugs like paraldehyde and anesthetic gases are excreted by the lungs, others have important biliary excretion, but by far the most important excretory route when considering both parent drug and metabolites is the kidney. It is easiest to consider renal modes of elimination in terms of the kidney's physiologic functions of filtration, active transport, metabolism, and passive transport. Metabolism has been discussed previously. The other modes of elimination will be discussed in sequence.

a. Filtration

The determinants of a drug's capacity to be filtered are protein binding, molecular size and charge, glomerular integrity and the number of filtering nephrons.

Since only that amount of drug free in plasma can pass through a normal glomerulus, displacement of highly bound drugs from serum proteins can increase the amount eliminated in the urine. As discussed previously, the clinical importance of this phenomenon with phenytoin, valproic acid and coumadin relates to proper interpretation of their concentration in blood.

Effective molecular size has been shown to be a limiting factor for excretion of mixed and high molecular weight dextrans. The dextran 40 used clinically is actually a mixture of different molecular weight species; the high molecular weight species (approximately 70,000) is selectively retained because it cannot be filtered. Consequently, these preparations remain in patients for extended periods of time. Other drugs are small enough that there are essentially no size limitations to filtration.

The integrity of the glomerulus as a seive is disrupted in nephrotic syndrome. Drugs bound to albumin could be carried with the protein into the urine, enhancing renal elimination. This phenomenon has been shown to occur with phenytoin and clofibrate, but in the four patients studied the excretion rate was not increased enough compared to overall elimination to be important.

Most studies and clinical attention are directed to influences of decreased numbers of functioning nephrons on the renal elimination of drugs. The effect of decreased creatinine clearance on the elimination of digoxin and aminoglycoside antibiotics is particularly well known. In general, if 50% or more of the administered drug (or its active metabolites) is eliminated unchanged in the urine, decreased renal function will importantly change handling of the drug and require dose adjustment. An approach to dose adjustment is presented in the second section of this protocol.

b. Active Transport

The renal tubule can both actively secrete and actively reabsorb a variety of substrates. Active reabsorption appears to be inconsequential except for iodipamide (a cholecystographic agent)

which can induce marked uricosuria, presumably by decreasing the active reabsorption of uric acid in the proximal tubule. The uricosuria could be etiologic to the acute renal failure occasionally reported with this contrast agent. The same mechanism accounts for the uricosuria caused by probenecid, high dose salicylates and high dose phenylbutazone.

The uptake by pinocytosis from the proximal tubular lumen of gentamicin and other aminoglycoside antibiotics might be considered another example of active reabsorption. Originally it was felt that different capacities for uptake, or egress from the tubular cells after uptake determined the potential for nephrotoxicity of aminoglycosides; those which tended to accumulate within the cell being most toxic. More recent evidence has implicated that the potential for nephrotoxicity is more related to the ability of the particular aminoglycoside to disrupte lysosomal function once it has gained access to the interior of the cell.

The pars recta (straight segment) of the proximal tubule actively secretes into the tubular lumen a variety of organic acids and bases. The pathways for acids and for bases appear to be separate but within a group there is lack of specificity such that a variety of organic acids can compete with each other for transport as can a variety of organic bases.

A clinically important drug transport which is not of acids or bases is a secretory component of digoxin and digitoxin elimination which can be competed for by spironolactone and quinidine. Patients

coadministered these drugs will develop higher serum levels of cardiac glycoside. The site of digitalis transport appears to be the distal nephron.

1. Organic Acid Transport

The following table shows a list of organic acids with potentially important renal secretion:

ORGANIC ACIDS WITH A CLINICALLY IMPORTANT COMPONENT OF ACTIVE TRANSPORT

p-Aminohippurate
Cephalosporins
Diphylline
'Loop' Diuretics
Methotrexate
Nonsteroidal Antiinflammatory Agents
Penicillins
Salicylates
Sulphonamides
Sulphonylureas
Thiazide Diuretics

The different compounds in this table can compete with each other for secretion. This fact is used to therapeutic advantage in the treatment of gonorrhea, in which probenecid pretreatment causes the subsequently administered penicillin to be secreted more slowly resulting in higher and more sustained concentrations of penicillin in blood. Although all of the drugs listed this table have the potential to compete with each other, the degree to which they will compete is impossible to predict <u>a priori</u>. Most clinicians are aware of the need to decrease the dose of methotrexate if probenecid is administered. Few are aware, with potentially disastrous consequences, of a possible similar need if other drugs listed in the table are administered with methotrexate.

"Idiopathic sensitivity" to methotrexate might well be due in some cases to coadministration of inhibitors of the active secretion of methotrexate. A similar scenario could be postulated for combinations of any of the drugs listed in the table.

Another clinically important example of competition for transport is that which occurs between a variety of drugs and the accumulated endogenous organic acids of uremia. In fact, in mild to moderate renal failure, this mechanism is probably more important than is decreased nephron mass for the decreased elimination of a number of organic acids. Organic acid diuretics such as furosemide, ethacrynic acid, thiazides, metolazone, etc., reach their site of action by secretion into the lumen by the organic acid transport pathway. Accumulated organic acids in uremia block the access of these diuretics to their active site accounting for the requirement for larger doses of organic acid diuretics needed to attain amounts within the tubular lumen sufficient to cause a diuresis.

2. Organic Base Transport

The active transport system for organic bases and its importance in man is less well understood than is that for organic acids. The following table lists bases which have been shown to undergo potentially clinically important active secretion:

ORGANIC BASES WITH A CLINICALLY IMPORTANT COMPONENT OF ACTIVE TRANSPORT

Amantadine
Cimetidine
Ethambutol
Mecamylamine
Mepacrine (Quinacrine)
N-Methylnicotinamide
Procainamide
Pseudoephedrine
Tetraethylammonium

It has been assumed that organic bases can compete with each other for secretion as do acids, but such an interaction has never been documented clinically. Consequently, its importance in man is unknown. Recent evidence indicates that there may be several different base transport systems that do not cross-compete. Because our understanding of the base transport system is so rudimentary it is impossible to speculate about its importance, though clinicians should be aware of the potential for interactions of drugs within this group.

c. Passive Transport

Weak acids and bases can be passively reabsorbed in the collecting duct. For this to occur, these drugs must gain entry to the tubular lumen in the proximal portion of the nephron either at the glomerulus or by active secretion by the proximal tubule. Even drugs with high rates of proximal entry can be almost completely reabsorbed in the collecting duct. Passive reabsorption is modulated by urinary pH and flow rate.

1. Urinary pH

The effect of urinary pH is related to the principle of passive nonionic diffusion which is based on the premise that a non-ionized molecule more readily passes across a lipid membrane than does its ionized congener. Consequently, the effect of urinary pH on the relative amount of ionized component decreases, and excretion decreases. Not all weak acids and bases demonstrate urine pH dependent elimination; one cannot assume that these principles will apply to all weak acids and bases. Part of the lack of effect with some drugs pro-

bably relates to the drug's pKa and the lipid solubility of the congeners. For example, if even the non-ionized species is poorly soluble in lipid, its ability to cross the tubular plasma membrane would not be enhanced. In this setting, changes in urinary pH would not cause changes in renal elimination.

Another modulator of the ability of the non-ionized congener's ability to pass across the lipid membrane may be antidiuretic hormone which can increase by 50-100% the ability of lipophilic compounds to pass across the toad urinary bladder, a structure functionally analagous to the mammalian collecting duct. These findings have not been extrapolated to studies in man. Other modulators of the effects of urinary pH on drug reabsorption are less well defined.

Urinary pH has been shown to be a clinically important determinant of elimination for the drugs shown in the following table:

COMPOUNDS WITH CLINICALLY IMPORTANT
URINE pH-DEPENDENT ELIMINATION

Weak Acids
- Phenobarbitone
- Salicylates
- Sulphonamide Derivatives
- Trimethoprim

Weak Bases
- Amphetamine
- Ephedrine
- Mexiletene
- Pseudoephedrine
- Phencyclidine (PCP)
- Quinine
- Tocainide
- Tricyclic Antidepressants

This importance for the weak acids, particularly phenobarbital and salicylates, is well known; that for weak bases less so. Alkalinization of the urine, by favoring excretion of the ionized congener of phenobarbital or salicylates, is a mainstay of therapy for toxicity due to these agents. It has also been demonstrated by that the small changes in urinary pH caused by modest doses of antacids can enhance the elimination rate of salicylate sufficient to prevent attaining concentrations in blood necessary for their anti-inflammatory effect.

The effect of urinary pH on the elimination of amphetamine may be better know to abusers of this drug than to clinicians. Since amphetamine is a weak base, alkalinizing the urine increases the amount unionized, favoring reabsorption. Amphetamine abusers regularly ingest baking soda before "shooting" to prolong the "high". Therapeutically, it would be important to acidify the urine of a patient with an overdose of amphetamines. Recently, a similar importance of urinary pH has been demonstrated with phencylcidine (PCP, "angel dust", etc.). The supposedly non-toxic pseudoephedrine has been shown to accumulate to toxic levels in children with renal tubular acidosis in whom a persistently alkaline urine favored passive reabsorpiton of the drug. A similar phenomenon occurs with tocainide, an orally available lidocaine-like agent, where the administration of bicarbonate decreased the elimination rate.

2. Urinary Flow Rate

Urinary flow rate can affect excretion of some drugs by decreasing the concentration gradient for reabsorption because the urine is dilute and by decreasing the time for drug to diffuse out of the urine.

Urinary flow rate has been shown to be an important determinant of elimination for chloramphenicol, ephedrine, phenobarbital, pseudoephedrine and theophylline. This phenomenon would probably be clinically important only in patients with high urinary flow rates for prolonged periods of time.

Clinicians seem to pay little attention to the importance of urinary pH and flow rate except in the case of salicylate or barbituate overdose. As discussed above, more thought should be given to the importance of the urine pH for excretion of a broader gamut of drugs as well as for clinical diagnosis.

3. Dialysis

Space does not allow discussion of the elimination of drugs by dialysis in great detail and in particular dialysis techniques, but it is important to review some of the more pertinent determinants of a drug's dialyzability.

a. Dialyzability

Molecular size can importantly influence a drug's dialyzability. In general, compounds of molecular weight less than 500 Daltons have flow dependent dialyzability, while elimination of larger drugs depends on dialyzer surface area. Vancomycin, with a molecular weight of 1800 Daltons, is big enough that it is not dialyzable. Other drugs for which molecular size is clinically important are amphotericin B, erythromycin, morphine, digoxin, and digitoxin, all of which have poor dialyzability that is limited by membrane surface area. All other drugs are small enough that their dialysance is determined by flow rate of blood and dialysate and other determinants to be dicussed subsequently.

For a drug to be dialyzable, it must be water soluble (this does not apply to resin hemoperfusion). Many of the sedative-hypnotics which are often seen in overdose settings such as glutethimide, methaqualone, meprobamate, ethchlorvynol, tricyclic antidepressants, etc. though of small molecular weight, are relatively insoluble in water and are poorly dialyzable by conventional hemodialysis. Resin or charcoal hemoperfusion is not dependent on water solubility and, therefore can remove these drugs effectively. In addition, drugs highly bound to serum proteins, in general, are poorly dialyzable. Again protein binding does not appear to be a limiting factor with sorbent hemoperfusion.

Whether or not dialysis can contribute importantly to a drug's removal from the body relates to that drug's intrinsic plasma clearance; namely, how fast the body can eliminate the drug exclusive of dialysis. For dialysis to add a clinically important increment to overall drug elimination, clearance by dialysis should increase overall clearance by approximately 30%. Some general principles can be appreciated by considering the determinants of the clearance of a drug. Clearance is equal to the product of the elimination rate constant and the volume of distribution:

$$Cl = K_e \times V_d$$

but K_e is related to half-life such that

$$Cl = 0.693\ V_d/T_{1/2}$$

From this relationship it is clear that if the volume in which a drug distributes is large, clearance is large, and for dialysis to add an important increment to clearance, dialyzability would have to be great.

This also makes intuitive sense in that a large volume of distribution means much of the body burden of the drug is in the peripheral tissues; dialysis can only remove the amount in the blood; consequently, drug in the tissues is not accessible to the dialyzer, and the body burden of the drug is not importantly decreased by dialysis. The converse is true for a drug with a small volume of distribution unless it is highly protein bound and, thereby does not cross the dialysis membrane.

Similarly, if the half-life is short (i.e., elimination is fast) the intrinsic clearance is great and dialysis would be less likely to have an important effect. The converse is also true. The effect of dialysis on the clearance of aminoglycosides illustrates the validity of this concept. In a patient with normal renal function the half-life of an aminoglycoside antibiotic is relatively short (2 or 3 hours). Therefore, clearance is large and dialyzing such a patient would not remove important amounts of the drug. However, aminoglycosides have long half-lives in patients with end stage renal failure. Therefore, clearance is low and dialysis can eliminate enough of the antibiotic to require dosing after each dialysis.

b. Hemodialysis

When to use hemodialysis or hemoperfusion (vide infra) for patients with drug overdoses is often debated and must be highly individualized to both patient status and the capacities of one's hospital. For example, an identical patient might be treated differently depending on whether one's local expertise were pulmonary care versus technical skill in performing dialysis. We suggest in the following table a modification

of guidelines proposed by Schreiner all of which are predicated on the ability of dialysis to importantly contribute to elimination of the drug:

GUIDELINES FOR DIALYSIS OF THE POISONED PATIENT

1. Severe clinical intoxication with life-threatening cardiovascular instability despite adequate volume replacement.
2. Ingestion and probable absorption of a potentially lethal dose.
3. A blood level of the drug which is in a range resulting in considerable mortality.
4. Impaired ability to eliminate the drug by endogenous routes either by disease itself, toxicity of the drug, or by saturation of pathways of elimination.
5. Prolonged coma if respiratory care is inadequate.
6. Methanol or ethylene glycol ingestion.

Methanol and ethylene glycol ingestion warrant more detailed comments, for poisoning with either of these two agents is a clear indication for hemodialysis. Toxicity of massive doses can be completely prevented by appropriate treatment. Both methanol and ethylene glycol are benign and their toxicity is mediated by metabolic byproducts. The first step in the metabolism of both of these compounds is alcohol dehydrogenase for which ethanol is a preferred substrate. Consequently, adequate therapy entails not only hemodialysis to remove the parent methanol and ethylene glycol and any metabolites which may have formed, but also administration of sufficient ethanol to block further formation of the toxic metabolites. The latter can be complicated, for ethanol itself is dialyzable and its infusion rate must be adjusted to maintain enzyme-blocking serum concentrations of ethanol (target concentration = 100 to 200 mg%). In addition, chronic drinkers have a higher capacity to metabolize ethanol and require

higher maintenance infusion rates, unless, of course, they have liver disease. Clearly, the ethanol dose must be individualized and followed with serum concentrations if possible. The following table presents recommendations as a first approximation of the required ethanol dose. Hemodialysis for 4 to 6 hours appears sufficient for treatment of even massive overdoses. Ethanol infusion should probably be continued for up to 24 hours:

DOSE OF ETHANOL FOR ACHIEVING A TARGET CONCENTRATION OF 100 MG% IN THE TREATMENT OF METHANOL OR ETHYLENE GLYCOL INGESTIONS

Loading Dose	0.6 g/kg
Maintenance Dose:	
Nondrinkers	66 mg/kg/hr
Chronic Drinkers	154 mg/kg/hr
During Hemodialysis*	170 mg/kg/hr

* This value is intermediate between that recommended by McCoy et al. (1979) and Peterson et al. (1981). The same results can be achieved by maintaining a dialysate ethanol concentration of 100 mg%.

c. Hemoperfusion

Recently, attempts have been made to increase the dialyzability of water insoluble drugs that are severely toxic in overdose settings. Resins or activated charcoal have been used to bind these drugs and irreversibly extract them from the patient's blood. It is clear that these drugs can be removed efficiently by resin hemoperfusion. In fact, dialysis clearance for many of them is equal to blood flow through the dialyzer. Unfortunatley, however, these drugs have large volumes of distribution so that the maximal reduction in blood concentrations of

many or most of these drugs is only short-lived, and the drug stores in peripheral tissues serve as a reservoir to refill the blood with drug as soon as hemoperfusion is stopped. In addition, the procedure itself causes decrements in circulating formed elements in the blood. Though newer generation columns appear to be safer, one can still anticipate a 30 to 40% decrease in platelet count after 4 hours of hemoperfusion. It is likely that clearer indications for use of resin hemoperfusion will evolve. At present, the general indications for dialysis for poisoning listed previously would also apply for hemoperfusion realizing that hemoperfusion has been demonstrated to remove important amounts of the drugs listed in the following table in overdose settings:

DRUGS FOR WHICH RESIN HEMOPERFUSION HAS BEEN DEMONSTRATED TO REMOVE CLINICALLY IMPORTANT AMOUNTS

Barbiturates
Chloral Hydrate (Trichlorethanol)
Chloroquine
Digitalis Glycosides
Ethchlorvynol
Glutethimide
Meprobamate
N-Desmethylmethsuximide
Salicylate
Theophylline
Tricyclic Antidepressants

D. Dosing Interval

Dosing interval and dosing regimens will be dicussed in the second section of this protocol.

III. EFFECT OF THE KIDNEY ON THE DISTRIBUTION OF DRUGS TO TISSUES

Changes in the distribution of a drug that affect the relationship between dose and its concentration in blood were discussed previously. In other circumstances there occur changes in distribution of a drug in which the concentration in blood is the same but the response to that concentration is altered. This phenomenon should not be construed as a change in "sensitivity" to the drug, for it probably more represents a change in distribution of drug in peripheral tissues that favors more drug reaching its site of action, the relationship between concentration at the site of action and effect remaining the same.

Uremia or alterations in systemic pH appear capable of changing access of a drug to its site of action. In uremia, the change in albumin binding of diazoxide increases the antihypertensive effect though the total concentration of diazoxide in blood remains the same as in non-uremic patients. A similar phenomenon occurs with thiopental anesthesia. The dose needed for attaining a certain level of anesthesia is less in subjects after urea infusion, or, considered in another light, the same concentration of anesthetic causes more depression of consciousness in subjects administered urea than in normals.

Changes in systemic pH can also affect distribution of a drug to a site of activity without changing concentrations in blood as has been demonstrated with salicylates, phenobarbital, and mecamylamine. Salicylates and phenobarbital demonstrate increased distribution into the central nervous system during acidemia. Central nervous system toxicity

is increased during acidemia at any given blood concentration of either of these drugs. It appears that acidemia favors the non-ionized species allowing diffusion of more drug into the CNS. This phenomenon has been documented in pediatric patients in which acidemia causes increased delivery of salicylate into the cerebrospinal fluid. Consequently, an important part of therapy of salicylate or phenobarbital toxicity would be correction of a systemic acidemia.

IV. EFFECT OF RENAL FUNCTION ON SENSITIVITY TO DRUGS

Whether renal function can modulate "sensitivity" to drugs is unclear. Supposed instances of increased "sensitivity" may, in fact, represent changes in distribution or access of drug to its site of action. For example, the effect described earlier of thiopental in patients with uremia was originally felt to represent changes in sensitivity, but further scrutiny showed the effect to be one of distribution rather than of changing the relationship between drug concentration at the active site and response.

The acidemia of uremia and/or renal tubular acidosis may cause resistance to the pressor effects of catecholamines. This phenomenon may be a true example of changes in sensitivity.

Electrolyte and acid-base abnormalities due to renal dysfunction can affect "sensitivity" to drugs which affect the cardiovascular system. Hyperkalemia slows conduction throughout the heart and predictably increases the similar effects on conductivity of digitalis glycosides,

quinidine, procainamide, disopyramide, phenothiazines, and tricyclic antidepressants. Alaklosis, magnesium or potassium depletion, and hypercalcemia increase the sensitivity to the toxic effects of digitalis glycosides. Some investigators feel that decreased potassium increases digoxin availability to its site of action; if this does occur, sensitivity has not changed but the relationship has changed between concentrations of digoxin in blood and that at the active site. Whether the other conditions predisposing to digitalis toxicity represent true changes in sensitivity is unclear. Uremia appears to increase the sensitivity to pindolol in that blockade of exercise-induced increases in heart rate occurs at lower serum concentrations of pindolol than required in normal subjects.

The exact mechanism by which changes occur in response to a given amount of drug in blood is moot compared to the importance of realizing its occurrence in clinical settings. If the drug concentration in blood may not closely relate to response, clinicians cannot rely on measures of drug levels as therapeutic guidelines. One must follow clinical end points to assess response.

The kidney can influence the disposition and response to drugs in many ways. Categorizing and cataloguing these effects are helpful in sorting out the complexities of the kidney's role in handling of drugs. A better understanding of the multiplicity of effects of the kidney should help clinicians better recognize and be more able to anticipate changes from "normal" in response to or handling of drugs. By so doing, they should be able to improve drug efficacy and decrease toxicity.

Since changes in renal fuction can affect handling of a drug in many different ways, the clinician must understand not only the patho-physiology of his patient's disease but also the pharmacology of the drugs being used so he can assess clinical end points of efficacy and toxicity as a guide to therapy.

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ADJUSTING DRUG REGIMENS IN PATIENTS WITH RENAL DISEASE

I. INTRODUCTION

The medical literature is replete with guidelines for dosing drugs in patients with renal disease. Several different methods have been proposed with advocates and criticisms of all. At one extreme are publications testifying to the accuracy and predictability of a particular nomogram in allowing attainment of a desired concentration of drug. At the other extreme are examples of inaccuracies and poor predictability leaving the clinician with little confidence in the ability of nomograms to allow attainment of desired concentrations in his individual patient. As a result, the clinician is left with the dilemma of not knowing which guideline to use, and if he uses one, how much he can trust it. Clearly, measuring concentrations of drug facilitates attainment of desired concentrations in individual patients. However, obtaining such measures is impractical or impossible in many settings. Following clinical endpoints of pharmacologic effect, both efficacious and toxic, are invaluable in guiding drug therapy, but in many circumstances the clinician must place his faith in and entrust his patient's well-being to one or another guideline of drug dosage.

In this section, we will briefly discuss pharmacokinetic terms and principles which will be used in a more detailed analysis of the goals and principles of design of dosing adjustment in patients with renal disease. If used with an understanding of their limitations, dosing guidelines can be extremely useful. The goal of this section is to

clarify the characteristics of a dosing regimen that make it useful or not by focusing on methods of dose adjustment for aminoglycoside antibiotics, because their narrow therapeutic index, kinetic characteristics, and total dependence on the kidney for elimination dictate the greatest amount of precision of dose adjustment of any drugs in our armamentarium. The reader may then apply these principles in assessing current and future dosing guidelines.

II. TERMINOLOGY

Though the mathematical derivation of pharmacokinetic parameters can be quite complex, the concepts are relatively simple. Most clinicians are comfortable with the concept of a drug's half-life, $t_{1/2}$, which is the time required for the concentration of drug to decrease by half. Many dosing guidelines use half-life in their terminology while others use elimination rate constant, K_e. These two parameters can be used interchangeably since they are reciprocally related:

$$t_{1/2} = \frac{0.693}{K_e} \text{ or } K_e = \frac{0.693}{t_{1/2}}$$

Both these parameters are determined by graphic or computer analysis of the linear, terminal segment of a plot of the logarithm of the concentration of drug versus time. The slope of this segment is equal to $K_e/2.303$ when the serum concentrations are plotted as logarithm to the base 10 in the graphic analysis.

The volume of distribution of a drug, V_d, is an experimentally derived value without physiologic meaning. It relates the concentration of drug achieved to the amount of drug in the body:

$$V_d = \frac{\text{amount of drug in the body}}{\text{drug concentration}}$$

The clearance of a drug, Cl, is analagous to use of the term clearance in any other medical or scientific application. Clearance represents the amount of blood, plasma or serum from which drug is totally removed per unit time. Consequently, a blood clearance of 100 ml/min means all the drug is removed from 100 ml of blood in one minute. Clearance, then, represents the ability of the body to remove the drug and is a function of both the volume in which the drug distributes (or dissipates from the blood) and the elimination rate of the drug:

$$Cl = K_e \times V_d$$

These parameters, along with the dose of drug which enters the body, determine the concentration achieved and the rate of its decline. If a drug is administered repeatedly, the dosing interval, τ, also becomes important.

It may be easiest to conceptualize the interrelationships of these factors by considering the situation in which a patient has been receiving a drug for a sufficient period of time that he is at steady state. This occurs quickly if he has received a loading dose of drug and is then placed on a maintenance regimen. Otherwise, the time to reach steady state is four to five times the elimination half-life. At steady state the rate of drug entering the body is equal to the rate at which it is leaving:

$$\text{Rate In} = \text{Rate Out}$$

The rate of drug entering is, in turn, a function of the dose administered, the fraction, F, of that dose absorbed if administered orally or intramuscularly, and the time interval over which it is administered:

$$\text{Rate In} = F \times \text{Dose}/\tau \ ;$$

the rate of drug leaving the body is a function of its steady state concentration (Cp_{ave}) and its clearance:

$$\text{Rate Out} = Cp_{ave} \times Cl \ .$$

Therefore, at steady state

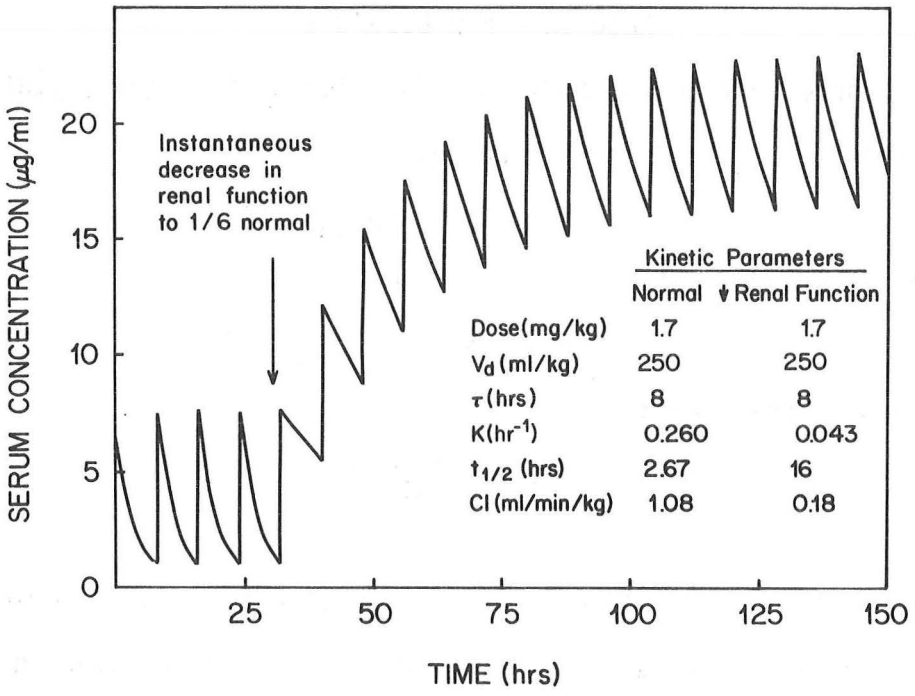
$$F \times \text{Dose}/\tau = Cp_{ave} \times Cl$$

or, rearranging the equation:

$$Cp_{ave} = \frac{F \times \text{Dose}}{\tau \times Cl}$$

Clearly, the steady state concentration of drug is an inverse function of dosing interval and clearance and directly related to dose. If drug clearance decreases as a result of decreased renal function as illustrated schematically in the following figure, a new steady state is attained after 4-5 times the new elimination half-life in which Cp_{ave} is increased by the same order of magnitude as the decrease in clearance.

EFFECT OF DECREASED RENAL FUNCTION ON
CONCENTRATION VS TIME PROFILE



Changes in dose, in dosing interval or in both can be used to compensate for changes in clearance and maintain Cp_{ave} the same as in patients with normal drug clearance. Dosing guidelines suggest changes in dose and dosing interval but additionally many guidelines attempt to quantitatively correlate an index of renal function such as serum creatinine or creatinine clearance with drug clearance at that level of renal function.

Two other pharmacokinetic parameters are important in considering dosing regimens; namely, Cp_{max}, the maximum or peak, and Cp_{min}, the minimum or trough, concentration. Both can be important determinants of efficacy and toxicity, as will be discussed in more detail subsequently. Additionally, in a patient receiving intermittent multiple dosing, Cp_{max} and Cp_{min} are the usual values measured when monitoring the patient with determinations of concentrations of drug in serum. The average serum concentration, Cp_{ave}, on the other hand is a theoretically calculated value which is not the geometric or arithmetic mean of maximum and minimum concentrations. It can only be directly measured if a patient is receiving a continuous intravenous infusion. Dosing nomograms can be designed to obtain a desired Cp_{max} or Cp_{min} as well as Cp_{ave}.

III. QUANTITATIVE DOSE ADJUSTMENT

As demonstrated in the previous figure, drug accumulation occurs in patients with renal failure and may cause toxicity. Quantitative dose adjustment is mandatory to avoid toxicity from a drug with a low therapeutic index and involves four steps: 1)Evaluation and quantitative estimation of renal function; i.e., glomerular filtration rate (GFR). 2)Estimation or prediction of the half-life of the chosen drug in that patient based on the estimated GFR and data from the literature relating drug half-life to renal function. 3)Choice of an appropriate dosing regimen of the drug with selection of dose and dosing interval to produce the desired predicted concentrations of drug in serum and time-course of these concentrations. 4)Use of measures of serum drug concentrations and assessment of clinical endpoints of pharmcologic effect to individualize the dosing regimen.

A. Determination of Creatinine Clearance as an Index of Renal Function

The most reliable way to determine creatinine clearance is by a carefully collected, timed urine specimen with a serum creatinine determined at the midpoint of the collection. However, because of the inherent difficulties and errors of urine collection, serum creatinine, rather than direct measurement of creatinine clearance, has been commonly used to estimate renal function. Several nomograms and formulas which consider age, sex and body weight are available to convert serum creatinine to creatinine clearance. Other nomograms have not considered these variables and, not surprisingly, are less accurate predictors of creatinine clearance than the nomograms accounting for age and weight of patients. A simple nomogram for bedside use to obtain creatinine clearance based on serum creatinine, age, sex and weight of a patient was published by Siersbaek-Nielsen and colleagues. This nomogram is widely used and appears to be very reliable. Cockcroft and Gault have published a formula estimating creatinine clearance from serum creatinine in an adult male:

$$Cl_{Cr} = \frac{140\text{-Age}}{Cr} \text{ ml/min/70 Kg body weight.}$$

The creatinine clearance for females is 85% of that for males. Creatinine clearances from this method are almost identical to those from the Siersbaek-Nielsen nomogram. The variability of values derived by this method compared to those from creatinine clearance determined with a urine collection was no greater than the variability between two separate,

direct measurements of creatinine clearance. This formula has been tested by other groups and found to be extremely reliable. However, accuracy becomes somewhat less as the serum creatinine exceeds 5mg%. Hull et al. have recently derived a formula with equal ease of use which appears to be equally accurate at low and higher levels of serum creatinine:

$$Cl_{Cr} = \frac{145\text{-Age}}{Cr} - 3 \text{ ml/min/70Kg body weight}$$

A limitation of using serum creatinine in these nomograms is that serum creatinine can correctly relate to renal function only during steady state with a stable serum creatinine. For practical purposes, one can assume stable renal function when clinical evaluation so indicates, and if two separate determinations of serum creatinine obtained at least 12 hours apart have values within 0.2 mg/dl.

A formula has been derived for calculating creatinine clearance when renal function is changing:

$$Cl_{Cr} = \frac{[293\text{-}2.03 \times age][1.035\text{-}0.01685(Cr_1+Cr_2)] + 49\frac{(Cr_1-Cr_2)}{\text{time in days}}}{Cr_1 + Cr_2}$$

(ml/min/70 Kg body weight)

This formula should only be used (if at all) to grossly approximate renal function and arrive at a starting point for adjusting therapy. Close assessment of the patient and measurement of drug blood concentrations should then be frequently monitored to guide further therapy.

It is important to note that many clinicians may need to somewhat reorient their thinking regarding magnitudes of change in creatinine clearance. For example, when considering the patient whose creatinine clearance decreases by 50% from 100 to 50 ml/min/1.73m^2, the clinician readily recognizes the magnitude of this decrement and its importance to therapy and drug dosing. On the other hand, a comparable percent decrease from 10 to 5 ml/min/1.73m^2 may be less readily appreciated, for both levels of renal function represent severe impairment and therapy would differ only a small amount if at all. However, such a change when used in a dosing nomogram mandates a large change in recommended dose or dosing interval, the neglect of which could result in toxicity or inadequacy of treatment.

In summary, by using the Siersbaek-Nielsen nomogram, the Cockroft and Gault formula, or the formula of Hull et al. one may estimate creatinine clearance from serum creatinine with a degree of reliability sufficient for clinical settings assuming serum creatinine is at steady state. If renal function is changing, one should directly measure creatinine clearance realizing that in such a setting any estimate is inherently less accurate. Despite creatinine clearance in many circumstances not being an accurate measure of absolute GFR, this flaw may be relatively unimportant since changes in creatinine clearance have been accurately and predictably correlated with changes in pharmacokinetics of specific drugs in patient populations.

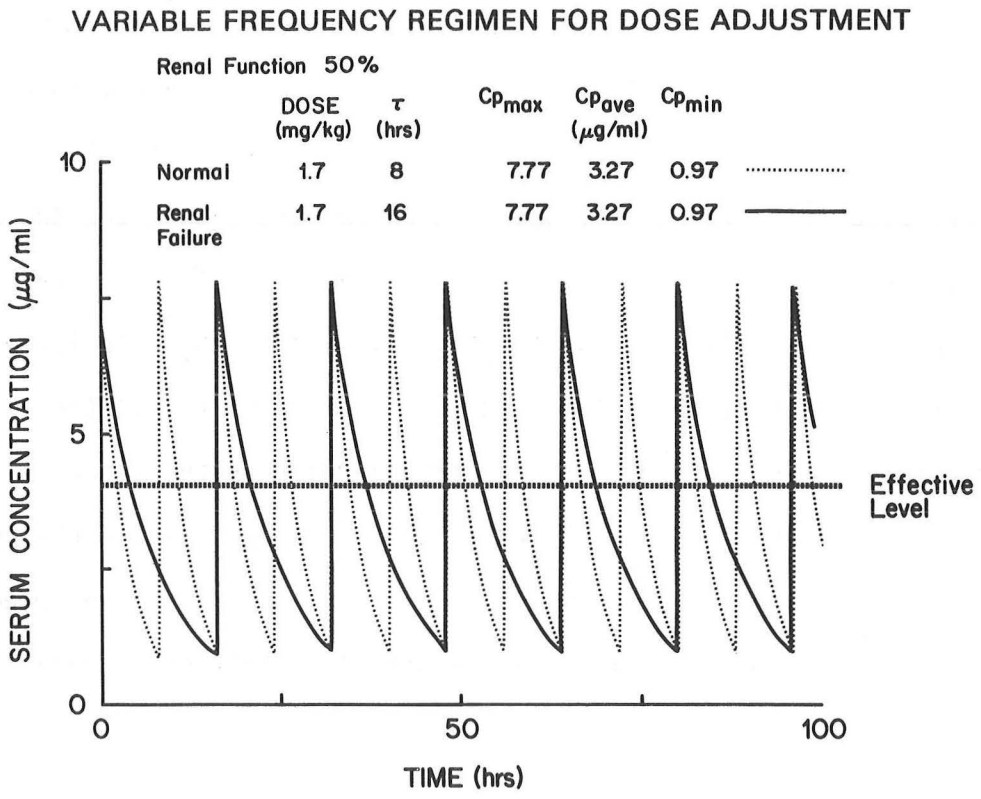
B. Choice of an Appropriate Dosing Regimen with Selection of Dose and Dosing Interval

After the elimination rate constant or half-life of the drug in an individual patient is predicted from a nomogram or tabulation, one must select a dosing regimen to produce the desired predicted concentration and the time course of the concentration of drug for that patient.

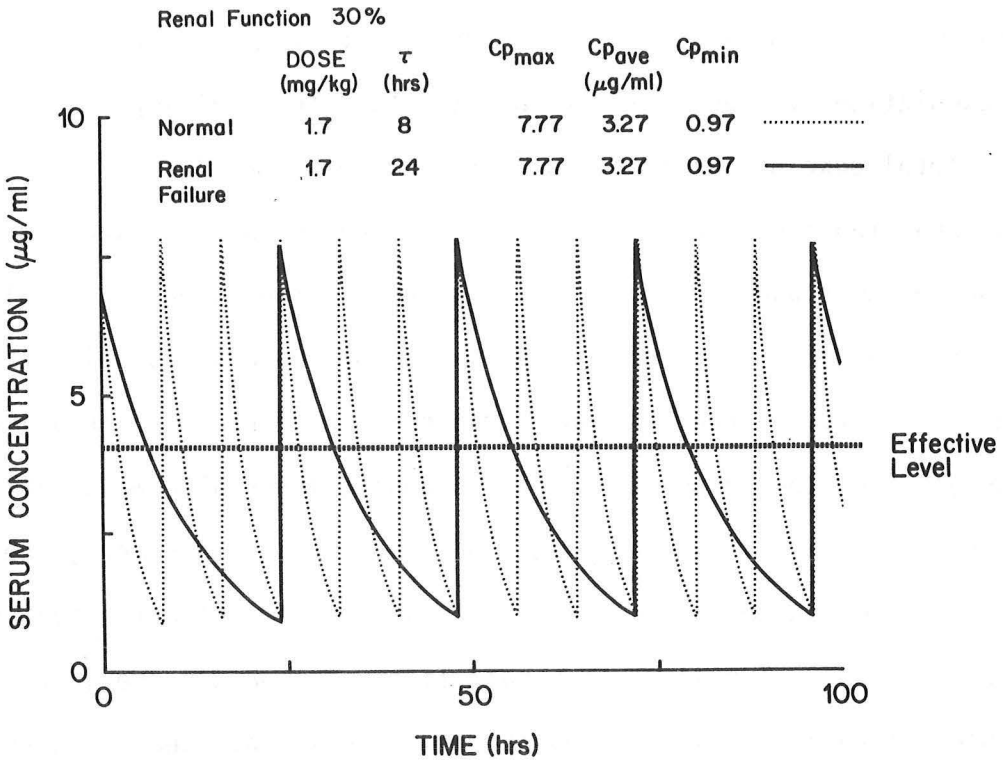
As with any dosing regimen, the objective is to achieve efficacy without toxicity. Precisely defining the pattern of concentration of drug versus time which accomplishes this objective is difficult, for with some types of drugs the goal is not well-defined even in patients with normal renal function. For example, it is debated in the infectious disease literature whether the objective of a dosing regimen is to maintain concentrations of antibiotic continually above the minimum inhibitory concentration (MIC), or the objective is to allow wide swings in concentrations from peak to trough with periods of time in which concentrations of antibiotic are less than the MIC. With cardiac glycosides, antiarrhythmics, antiepileptics, and theophylline the objective is more clearly to maintain trough concentrations within the therapeutic range. Most nomograms attempt to provide patterns of concentrations of drug in patients with renal dysfunction similar to those achieved in subjects with normal renal function. However, a change in the elimination rate of a drug causes a change from normals in the slope of the descent from peak to trough concentration. Consequently, a dosing regimen in a patient with decreased renal function will never produce a serum concentration vs. time curve identical to that of a subject with

normal renal function (with the exception of a continuous intravenous infusion).

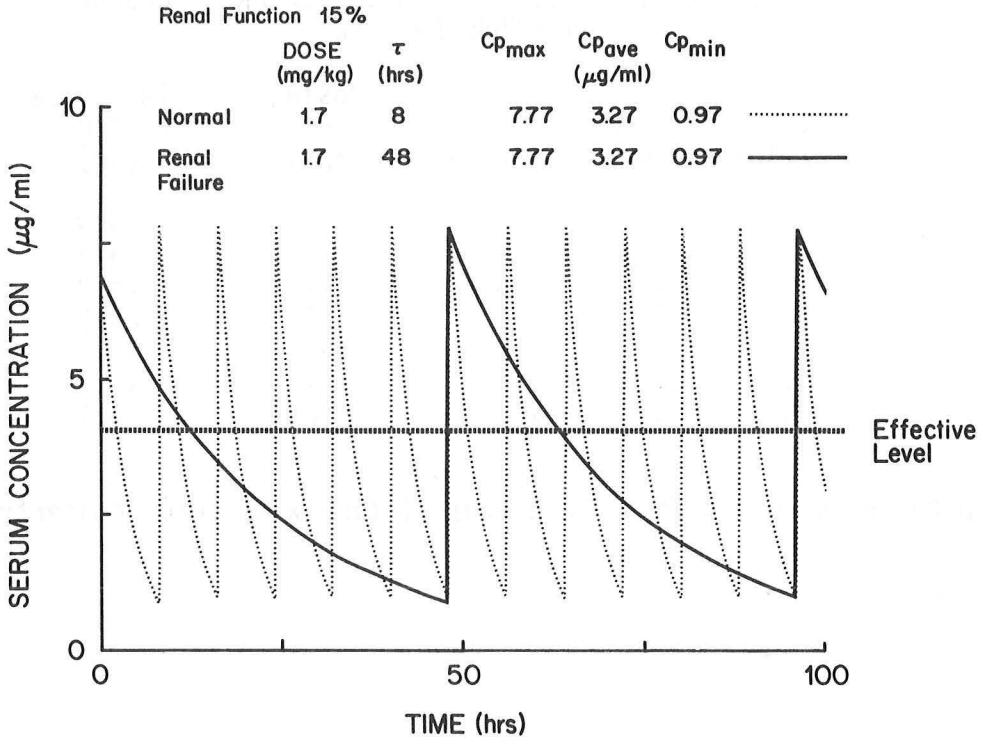
Several methods have been used to accomplish the objective of obtaining a serum concentration profile close to that in uncompromised patients. One method of dose adjustment is commonly referred to as the variable frequency regimen. This method in particular has been widely used for aminoglycoside dosing adjustment. A commonly cited nomogram used this method by recommending the same dose of gentamicin in patients with decreased renal function as in the uncompromised patient, administered at an increased dosing interval in direct relation to the prolongation of half-life of elimination. By so doing, Cp_{max}, Cp_{ave} and Cp_{min} remain the same as in patients with normal renal function as shown in the following schematics.



VARIABLE FREQUENCY REGIMEN FOR DOSE ADJUSTMENT



VARIABLE FREQUENCY REGIMEN FOR DOSE ADJUSTMENT



This method of dosing interval adjustment prevents toxicity caused by accumulation of drug in serum in patients with renal impairment, since the total dose administered is decreased in proportion to the decrease in renal function. However, as can be seen in these figures, as renal function decreases the amount of time during the dosing interval increases in which the serum concentration of the drug is below the minimally effective concentration. This phenomenon occurs with aminoglycosides and other drugs which have a dosing interval considerably less than their half-life. Using this method of dose adjustment, the duration of time in which the concentration is below the effective concentration increases with increasing half-life. As one can see in the following table, in patients with the worst renal impairment, serum concentrations remain below the effective concentration for prolonged periods of time:

EFFECT OF DOSING INTERVAL ON TIME OF SERUM CONCENTRATIONS OF GENTAMICIN BELOW A THERAPEUTIC LEVEL (4 µg/ml) IN PATIENTS WITH DIFFERENT DEGREES OF RENAL FAILURE

Cl_{Cr} (ml/min)	T 1/2 (hr)	Dose (mg/kg)	Dosing Interval (hr)	Time Below 4 µg/ml (hr)
90	3.0	1.0	8	6.3
48	3.9	1.0	10	9.9
49	3.7	1.0	14	14.0
20	12.2	1.2	32	28.6
17	16.6	1.1	46	37.6
19	22.9	1.3	64	42.7
90	3.0	1.7	8	4.1

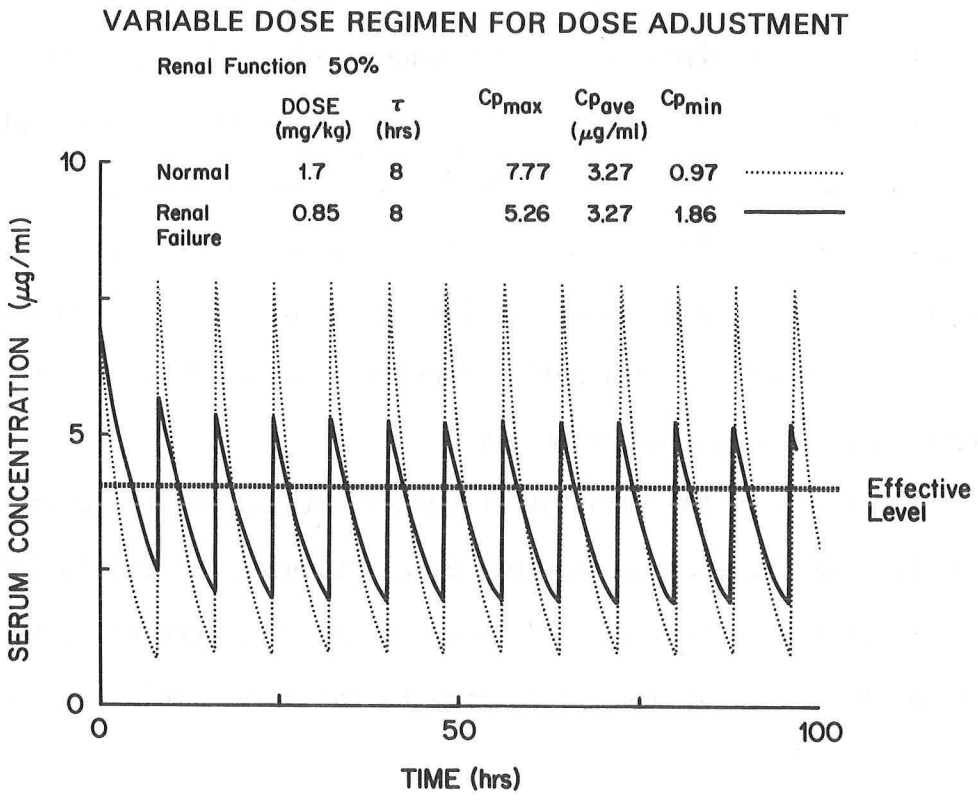
Despite an increased absolute amount of time with serum concentrations

above the effective level, the very long continuous time at subtherapeutic concentrations must be of concern to the clinician. Clearly, a longer period of time "subtherapeutic" might increase the likelihood of persistent infection when considering antibiosis, or of exacerbation of signs and symptoms of disease when considering other agents.

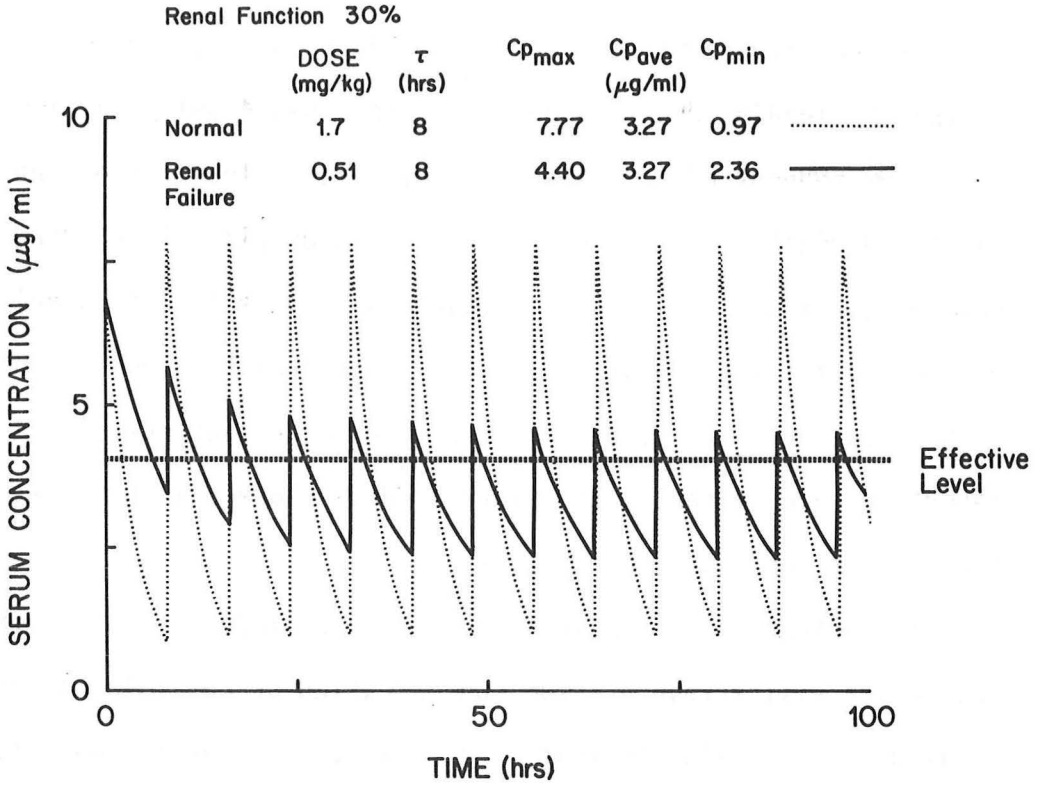
As a basic pharmacokinetic principle, the time during which the serum concentration is higher or lower than a fixed effective level is not only a function of half-life but also of dose. Increasing the dose of a drug will not only increase absolute serum concentrations but will also increase the amount of time spent above a chosen concentration as can be seen by comparing the last to the first row of the above table. However, increasing the dose to vary the amount of time above a selected effective level is limited by the narrow therapeutic ratio of many drugs including the aminoglycosides. For other drugs such as penicillins we have considerably greater latitude for increasing dose and the precision of dose adjustment can be less. It is not known what duration of sub-effective concentrations becomes critical for continued efficacy of the regimen. Clearly, however, most clinicians would feel uncomfortable with the prolonged subtherapeutic concentrations of drug that occur in patients with wide dosing intervals.

In contrast to the variable frequency method, several authors have suggested a variable dosage regimen by maintaining the dosing interval as in patients with normal renal function and by compensating for the decreased clearance of drug by decreasing the dose. This regimen results

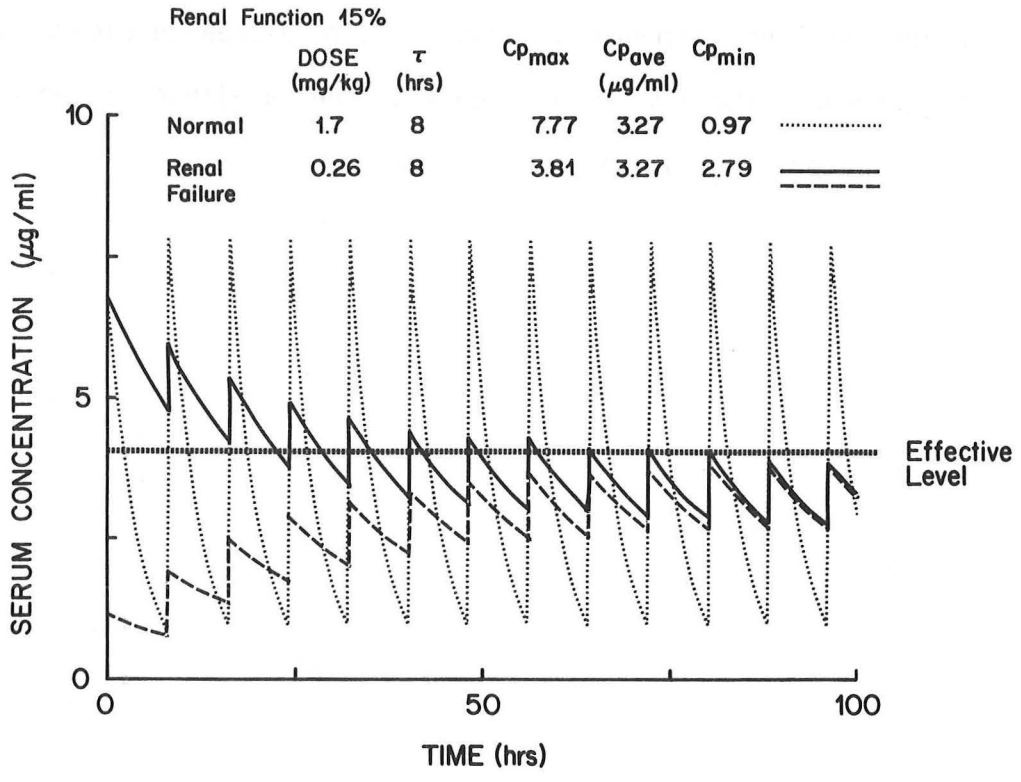
in the same Cp_{ave}, but Cp_{max} is lower and Cp_{min} higher than in patients with normal renal function. This regimen, as with the variable frequency regimen prevents drug accumulation, but in contrast, it avoids great fluctuations of serum concentration and theoretically could thereby avoid the prolonged duration of subeffective serum concentrations. However, as illustrated in the following three figures, with decreasing renal function the serum concentration may actually remain below the effective concentration at all times. This phenomenon occurs with a drug like gentamicin in which the dosing regimen in patients with normal renal function produces wide swings of serum concentration, with a Cp_{ave} below the effective concentration.



VARIABLE DOSE REGIMEN FOR DOSE ADJUSTMENT



VARIABLE DOSE REGIMEN FOR DOSE ADJUSTMENT

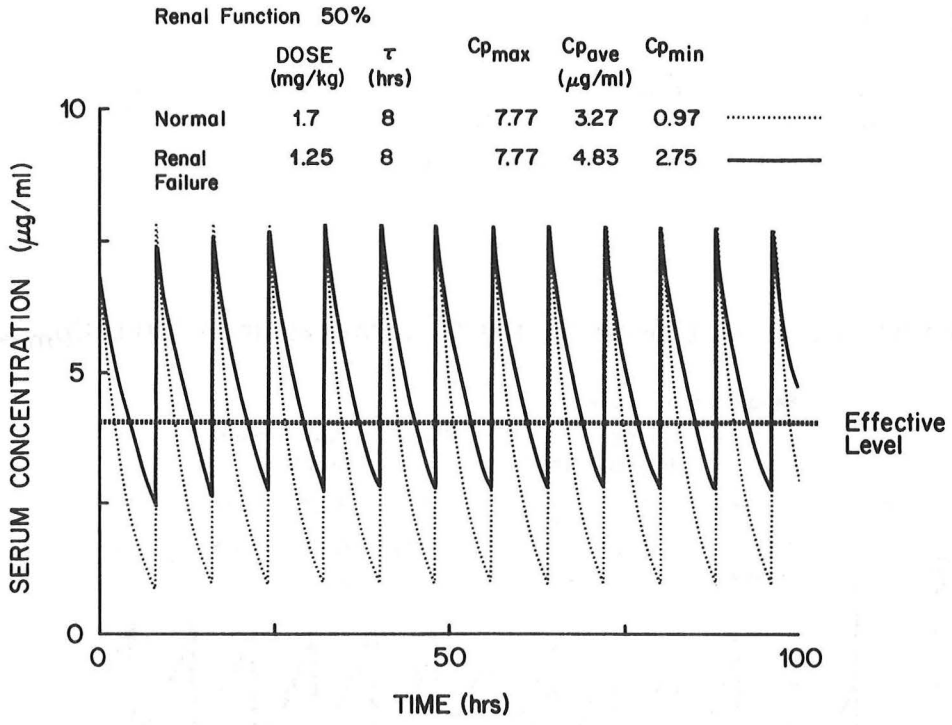


Another important consideration when using a variable dose regimen is that a "loading dose" is necessary to avoid a delay in time before the serum concentration reaches steady state. The last of the above figures demonstrates a serum concentration profile of this regimen when beginning administration with a maintenance dose (lower curve), as opposed to first administering a dose identical to a dose used in patients with normal renal function; a "loading dose" (upper curve). It is important to note that with a loading dose there will be a delay before the patient becomes "subtherapeutic".

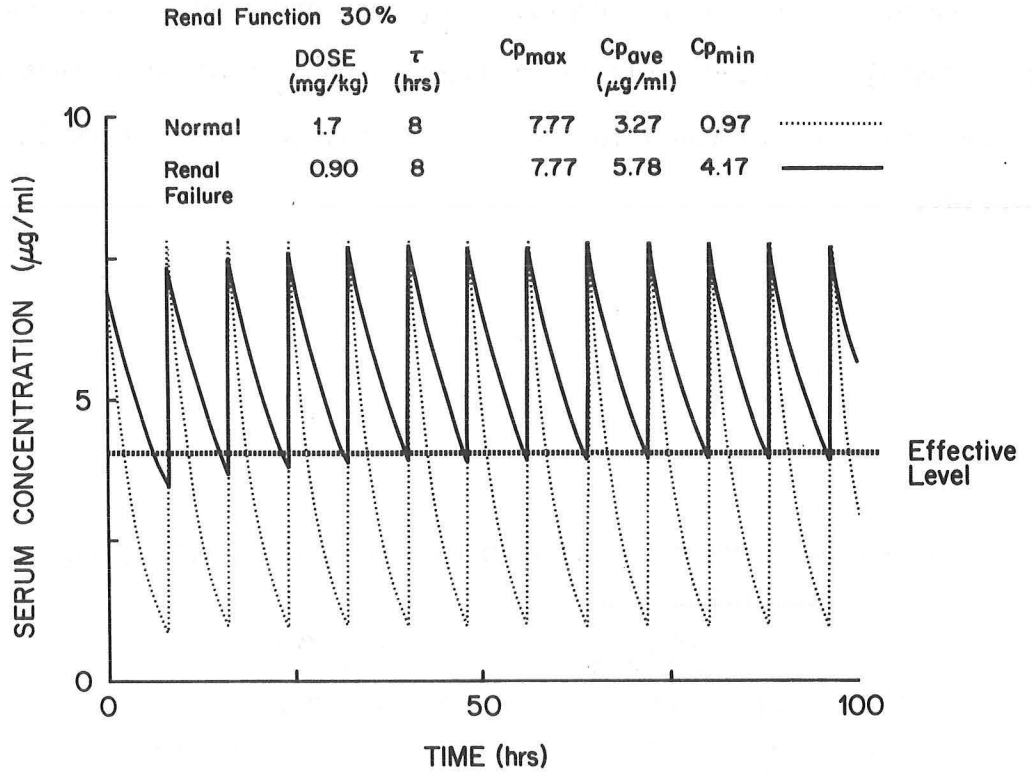
In another so called variable dosage regimen one can calculate a dose which will attain a serum concentration of Cp_{max} in patients with renal disease similar to that of a patient with normal renal function. Many nomograms, in fact, are calculated to achieve the same Cp_{max} in patients with decreased renal function as in those without renal impairment. In this situation the dose used in patients with renal failure will not decrease in proportion to decreased clearance of the drug, because the dose also depends on the magnitude of the chosen dosing interval relative to half-life.

The next three figures depict serum concentration vs. time curves for a dosing regimen calculated to obtain a Cp_{max} similar to that of patients with normal renal funtion and maintaining the same dosing interval.

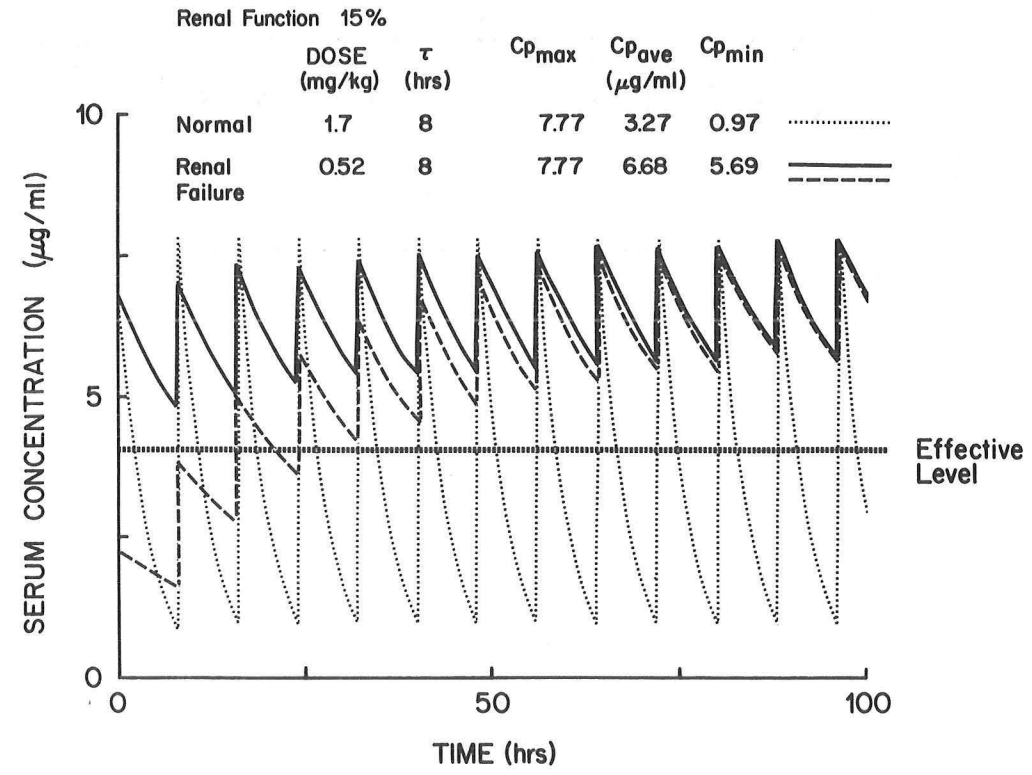
MODIFIED VARIABLE DOSE METHOD TO MAINTAIN A FIXED Cp_{max}



MODIFIED VARIABLE DOSE METHOD TO MAINTAIN A FIXED Cp_{max}

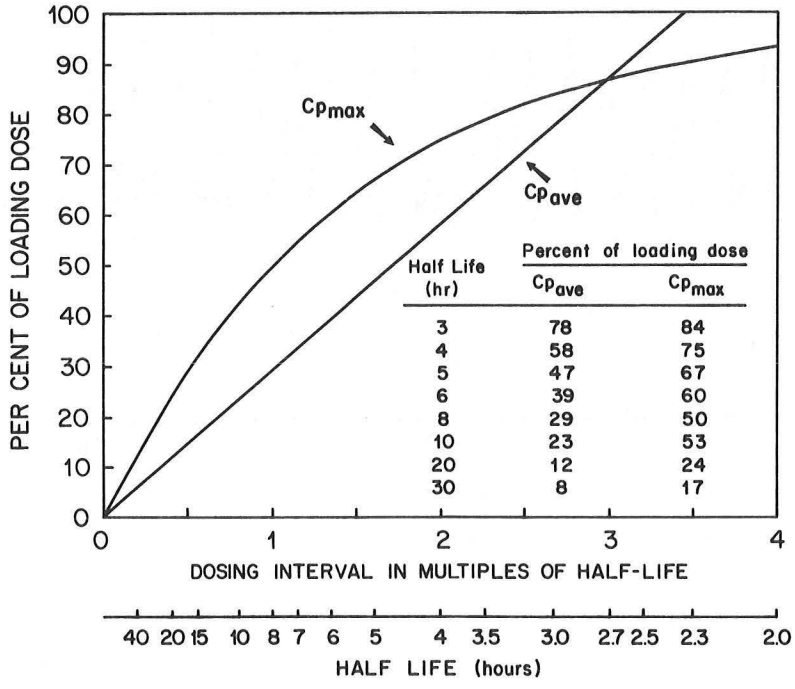


MODIFIED VARIABLE DOSE METHOD TO MAINTAIN A FIXED Cp_{max}

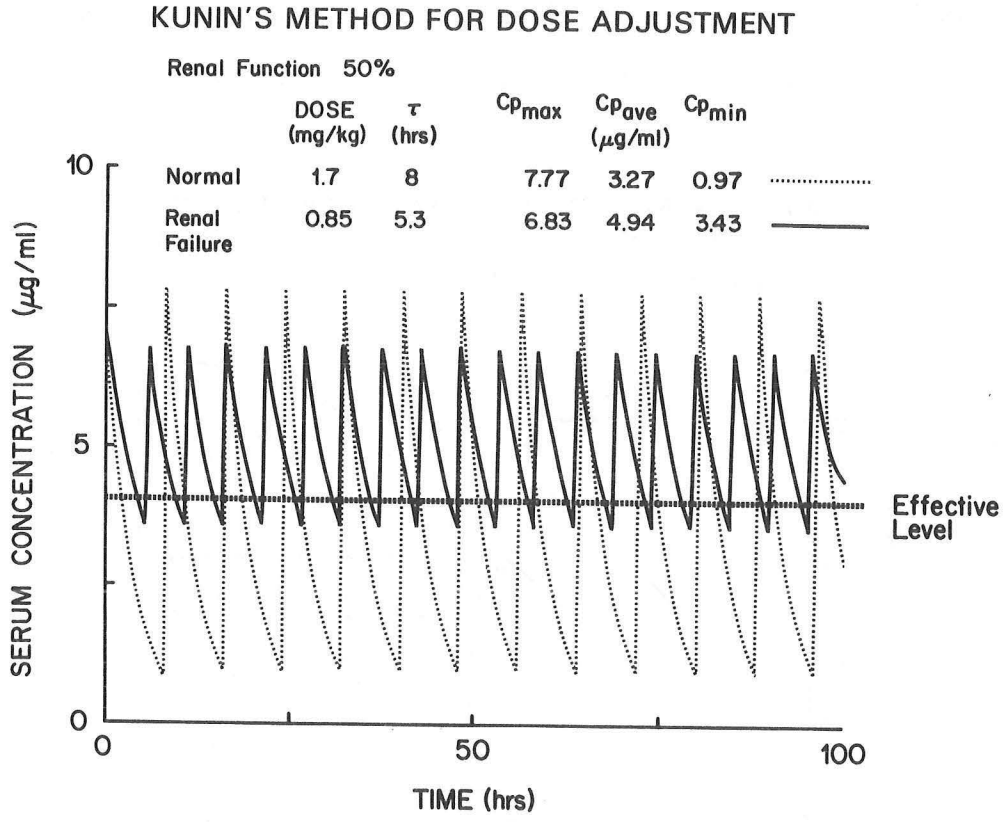


Again, the importance of "loading dose" is depicted in the last figure. Using this regimen, one can avoid subtherapeutic serum concentrations for patients with severe renal failure. However, using this regimen, the patient with the most compromised renal function is exposed to a progressively greater concentration of drug over time because the Cp_{min} is higher the worse the patients renal function. Consequently, to increase the amount of time with therapeutic concentrations of drug, one may have to subject the patient to greater risk, assuming risk is related to total drug exposure or related to cumulative trough concentration of drug in serum. Another impractical aspect of this regimen is that it is difficult to calculate the dose needed to maintain the same Cp_{max}. As shown in the following figure, there is a curvilinear relationship between the dose necessary and the peak drug concentration:

MAINTENANCE DOSES OF GENTAMICIN USED IN THE VARIABLE DOSE REGIMEN TO PRODUCE THE SAME Cp_{max} OR Cp_{ave} IN PATIENTS AS IN NORMALS



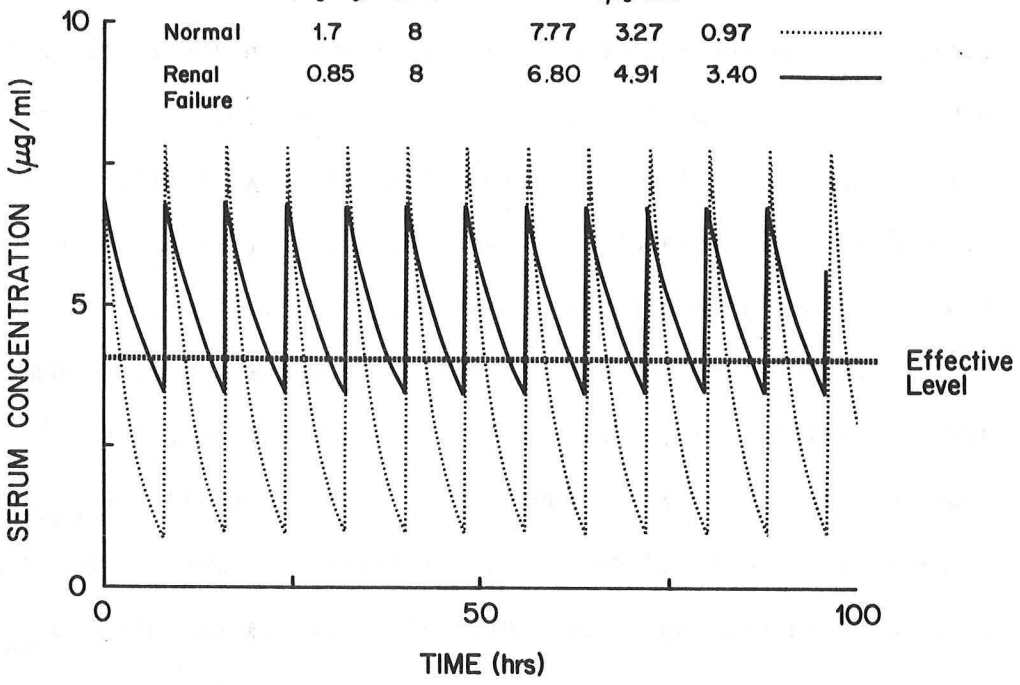
Another method of dosing, originally proposed by Kunin suggests one-half of the dose usually administered to patients with normal renal function given to the patient with renal failure at a dosing interval equal to the drug half-life. The following three figures show serum concentration vs. time curves using this method with the first dose of the drug being similar to that of normal subjects, i.e., a modified loading dose.



KUNIN'S METHOD FOR DOSE ADJUSTMENT

Renal Function 30%

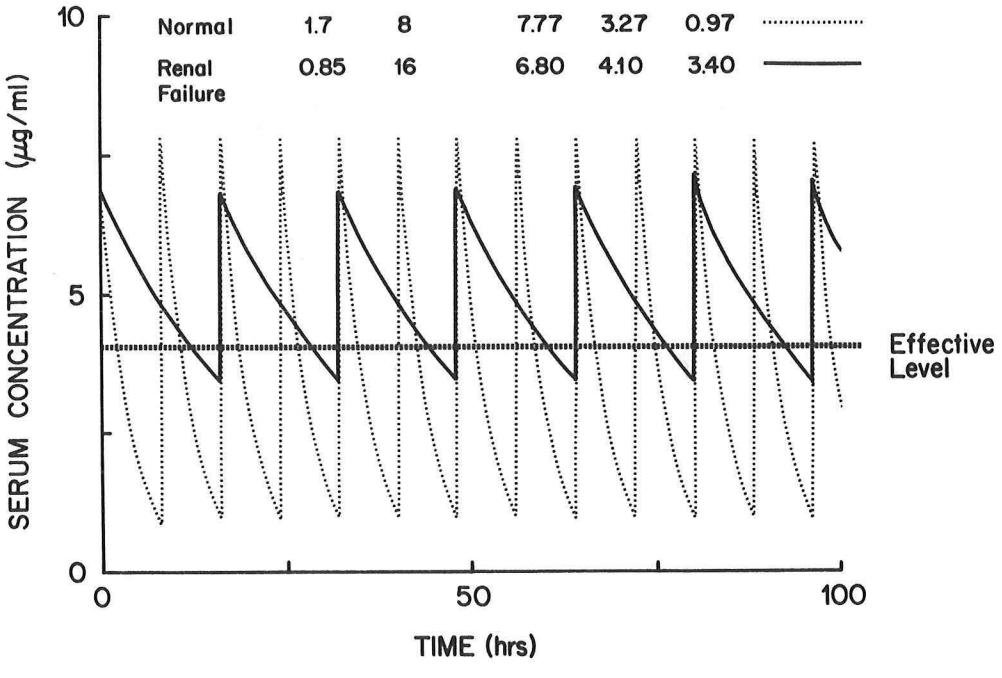
	DOSE (mg/kg)	τ (hrs)	Cp_{max}	Cp_{ave} (μg/ml)	Cp_{min}
Normal	1.7	8	7.77	3.27	0.97
Renal Failure	0.85	8	6.80	4.91	3.40



KUNIN'S METHOD FOR DOSE ADJUSTMENT

Renal Function 15%

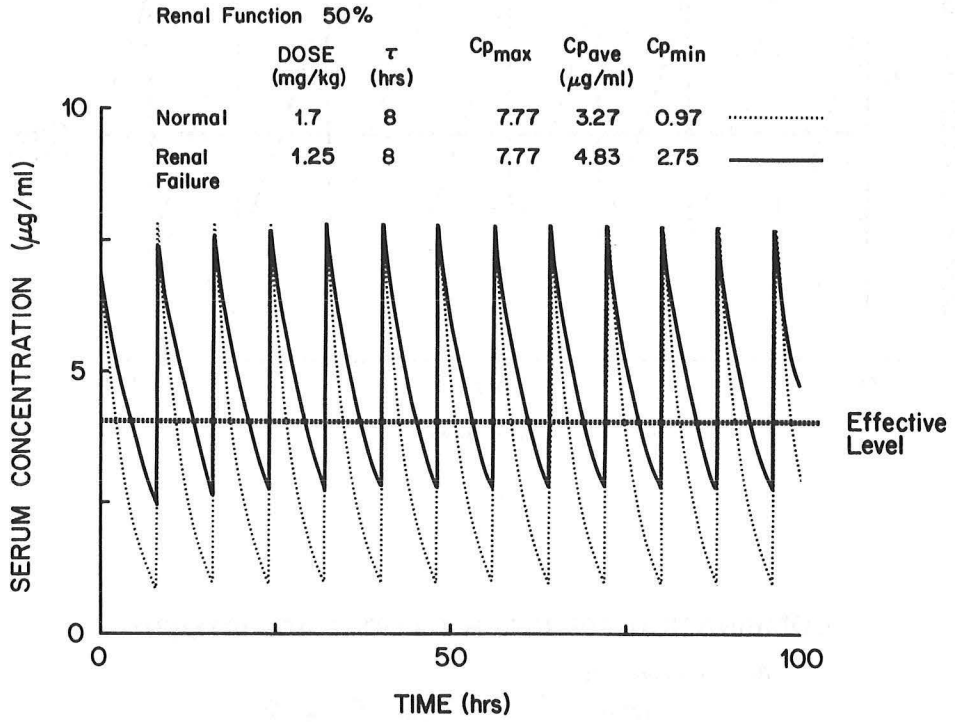
	DOSE (mg/kg)	τ (hrs)	Cp_{max}	Cp_{ave} (μg/ml)	Cp_{min}
Normal	1.7	8	7.77	3.27	0.97
Renal Failure	0.85	16	6.80	4.10	3.40



For a drug such as gentamicin which is normally given every third half-life, Kunin's method provides total doses higher than those in the variable frequency regimen. This may result in increased toxicity. A potential problem with Kunin's method is the "odd" dosing interval which may be impractical from a nursing point of view, particularly in patients with mild renal dysfunction. Overall, however, with severe renal disease, Kunin's method is practical and simple.

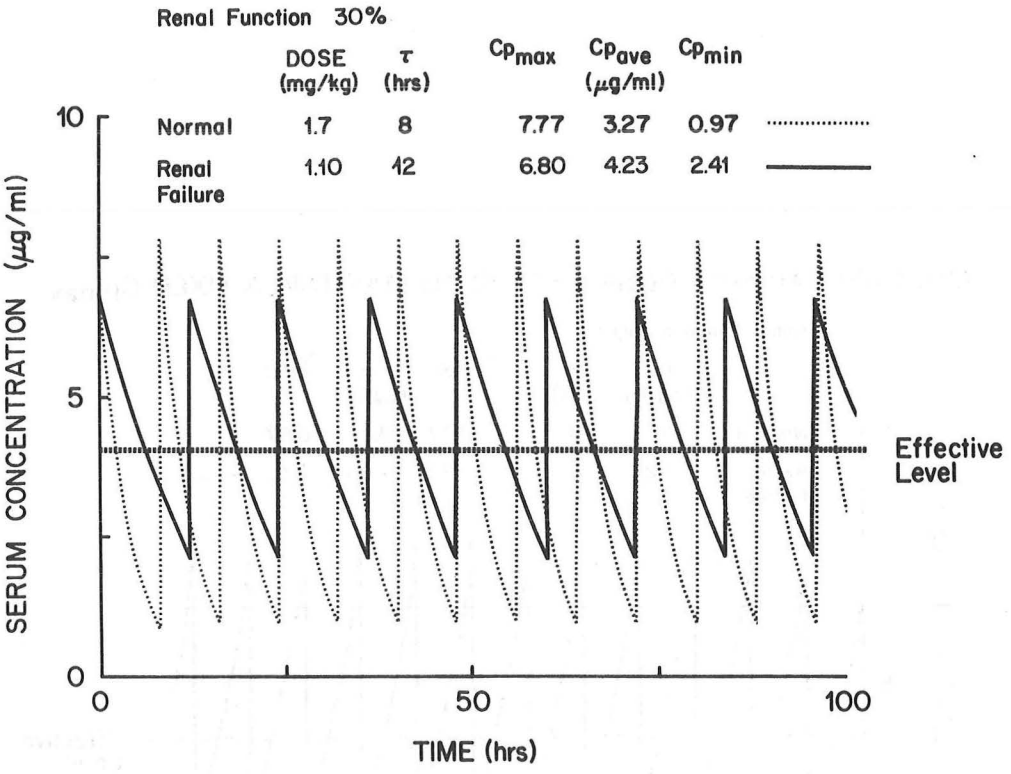
A combination approach has also been suggested for a number of drugs by Dettli and by Hull and Sarubbi suggesting a variable dose regimen for mild renal dysfunction to obtain a similar Cp_{max} to that in normals and a modified regimen in patients with more severe renal failure by increasing dosing interval, still maintaining Cp_{max}, but avoiding sustained, high trough levels of drug that may cause toxicity. For a patient with renal function 50% of normal, these guidelines would produce a pattern of response identical to that using the variable dose approach with a fixed Cp_{max} as shown again in the next figure:

MODIFIED VARIABLE DOSE METHOD TO MAINTAIN A FIXED Cp_{max}

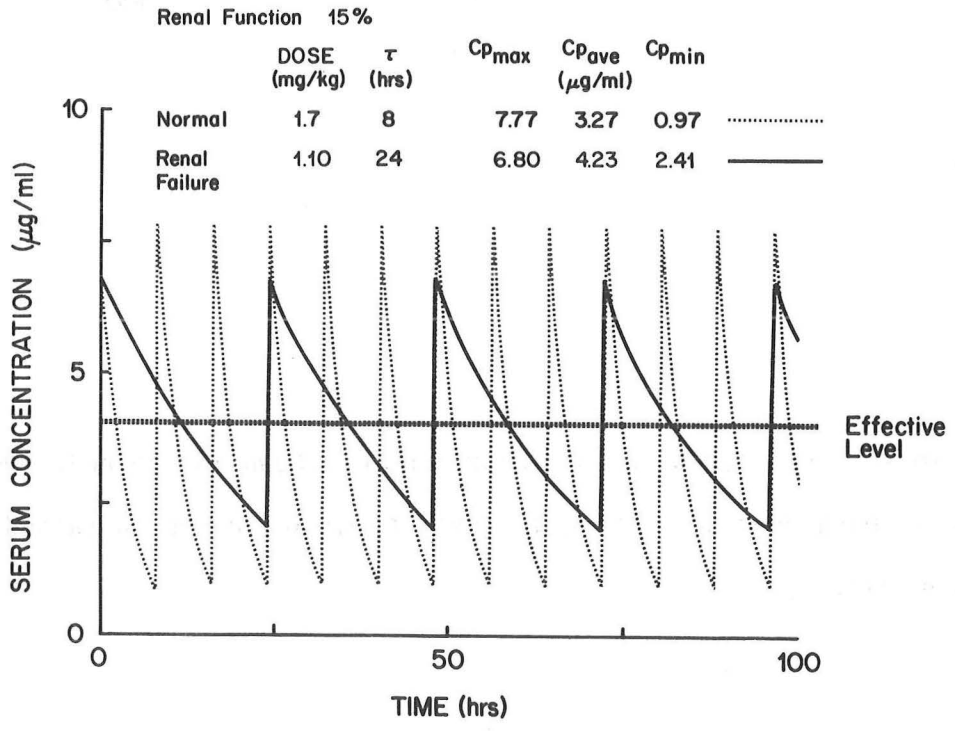


For worse renal function this approach, as shown in the next two figures, changes both dose and dosing interval to minimize the sustained trough concentrations.

COMBINATION APPROACH TO DOSE ADJUSTMENT



COMBINATION APPROACH TO DOSE ADJUSTMENT



The Hull and Sarubbi recommendations provide that as renal function worsens, the magnitude of difference between Cp_{max} and Cp_{min} becomes less, but Cp_{max} remains the same as in patients with normal renal function. The authors appropriately recommend increasing the dosing interval at severe degrees of renal impairment to avoid sustained high trough concentrations. This feature of the Hull and Sarubbi guidelines is its main advantage for aminoglycosides. The dosing interval should not be greater than 24 hours to avoid long durations of subtherapeutic serum concentrations.

In summary, different dosage regimens have advantages and disadvantages. There is no one universal dosing method which is applicable to all situations. A regimen is the best regimen for one drug at one renal function. The following table summarizes some of the advantages and disadvantages of the various general approaches. Dosing nomograms are subject to the errors of their assumptions and their data base emphasizing the need for close following of individual patients with measures of serum concentrations of drugs and evaluation of clinical endpoints of pharmacologic effect.

ADVANTAGES AND DISADVANTAGES OF GENERAL APPROACHES OF DOSING NOMOGRAMS

METHOD	ADVANTAGES	DISADVANTAGES
Variable frequency	1)Same Cp_{ave}, Cp_{max}, Cp_{min} 2)"Normal" dose 3)Ease of calculation	1)Possibly deleterious length of time subtherapeutic 2)"Odd" dosing interval causes potential for administration errors
Variable dose with fixed Cp_{ave}	1)Same Cp_{ave} 2)"Normal" dosing interval 3)Ease of calculation	1)Decreased Cp_{max} which may be continually subtherapeutic 2)"Odd" doses may lead to medication errors 3)Increased Cp_{min}- ? Increased toxicity
Variable dose with Fixed Cp_{max}	1)Same Cp_{max} - Attains therapeutic concentrations 2)"Normal" dosing interval	1)Increased Cp_{ave} , Cp_{min} - ? Increased toxicity 2)More difficult to compute dose
"Kunin" method	1)Same Cp_{max} - Attains therapeutic concentrations 2)Ease of calculation of both dose (fixed as ½ normal) and of dosing interval (every half-life)	1)"Odd" dosing interval 2)Increased dose for drug with half-life shorter than dosing interval in subjects with normal renal function 3)Decreased dose for drug with half-life longer than dosing interval in subjects with normal renal function
Combination	1)Can target same Cp_{max} 2)Can simultaneously change dosing interval and lessen impact of increased Cp_{ave} and Cp_{min} and possible toxicity	1)Need specific regimen for level of renal function and for each drug

We feel that the approaches of Dettli in general and that of Hull and Sarubbi for aminoglycosides are preferable, for they "individualize" therapy at different levels of renal dysfunction in an effort to maximize theoretical benefit and lessen the risk of potentially toxic serum concentrations. The clinician must be aware of the limitations of dosing guidelines. Nomograms cannot be used to abrogate the clinician of the responsibility to evaluate clinical endpoints of pharmacologic effect in each patient. He must realize that nomograms should be used as approximations. Their usefulness has limits, particularly in the patient with severe renal failure or in the patient with changing renal function when the patient may never be at steady state. When available, serum concentrations of drugs should be measured frequently but judiciously, for their use can clearly facilitate attaining a desired serum concentration. What concentration is desired may be yet another question and may vary among patients, thereby mandating frequent clinical assessment.

To most adequately adjust dosing regimens in any patient, one must quantitate disease severity, relate the disease severity to quantitative changes in drug handling and use feedback within the individual patient to arrive at precise dosing regimens. It would be virtually impossible for any clinician to serve as a repository for all of the data necessary to perform these steps. Moreover, once a drug blood concentration is obtained in an individual patient, the direction of a needed dosing change may be obvious but its magnitude less so. How can we accomplish the goals of having a readily accessible repository of data and formulas and the precision needed to individualize therapy? Currently, computer

technology would seem to be the best source. A clinician could access a computer by having a terminal on the ward, in the clinic or in the emergency room. He could seek information about the drug he intended to use and the computer would ask for patient data that would be important for handling of that drug. For example, it would seek information regarding renal function if the drug of interest were an aminoglycoside. From various algorithms programmed into the computer, a suggested dosing regimen could be derived which could then be implemented in the patient. Because of the considerable interindividual variability that exists, good therapeutics requires assessing the accuracy of a dosing regimen within the individual patient. Therefore, blood should be measured for drug concentrations which can be used as feedback (again using computer techniques) to "fine tune" therapy to the individual patient.

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