PHARMACOLOGIC ROLE OF THE KIDNEY

Medical Grand Rounds

Parkland Memorial Hospital

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D. Craig Brater, M.D.

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I. Introduction

The kidney is the major route of elimination for a wide variety of drugs. Table 1 shows a list of drugs with primarily renal elimination adapted from Prescott.

Cardiovascular Agents:
- Digoxin
- Procainamide
- Diazoxide
- Thiazide Diuretics
- Loop Diuretics
- Amiloride

Neural Agents:
- Barbiturates
- Amphetamine
- Tubocurarine
- Gallamine
- Neostigmine
- Atropine

Antibiotics:
- Aminoglycosides
- Penicillins
- Macrolides
- Cephalosporins
- Sulfonamides
- Tetracyclines
- Anti-Fungal Agents
- Ethambutol
- PAS

Oral Hypoglycemics:
- Sulfonylureas
- Phenformin

Table 1: List of drugs in which elimination by the kidney is primary

Though this list of agents is not comprehensive by any means, it is impressive in terms of the frequency with which the drugs in the list are used. It is likely, in fact, that many patients receive several of these

drugs. In addition to the drugs listed, one must consider that even those drugs not primarily eliminated by the kidney may be metabolized by the liver to compounds that themselves are active and may have an important component of renal elimination. For example, procainamide is acetylated in the liver 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.

Our knowledge of the kidney's contribution to drug elimination is expanding rapidly, especially regarding effects of changes in glomerular filtration on renal elimination of a number of agents. Less attention has been paid to other processes by which the kidney eliminates drugs such as active secretion and passive reabsorption. This discussion will encompass the variety of modes by which the kidney eliminates drugs and drug metabolites emphasizing those modes which have received less attention in the medical literature.

II. General Considerations

In simplest terms, considering the pharmacologic role of the kidney is essentially considering the different ways in which changes in renal function affect the relationship between the dose of a drug administered and the response to that drug. Figure 1 depicts a general schema by which one can subdivide the determinants of the relationship between dose and response and analyze them separately.

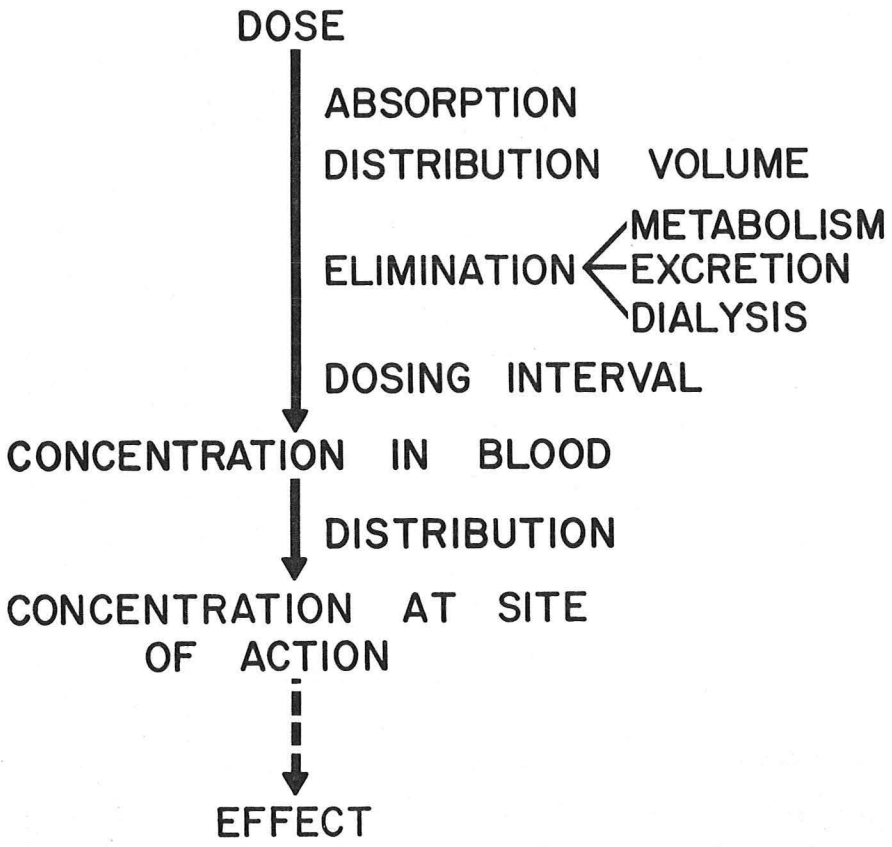


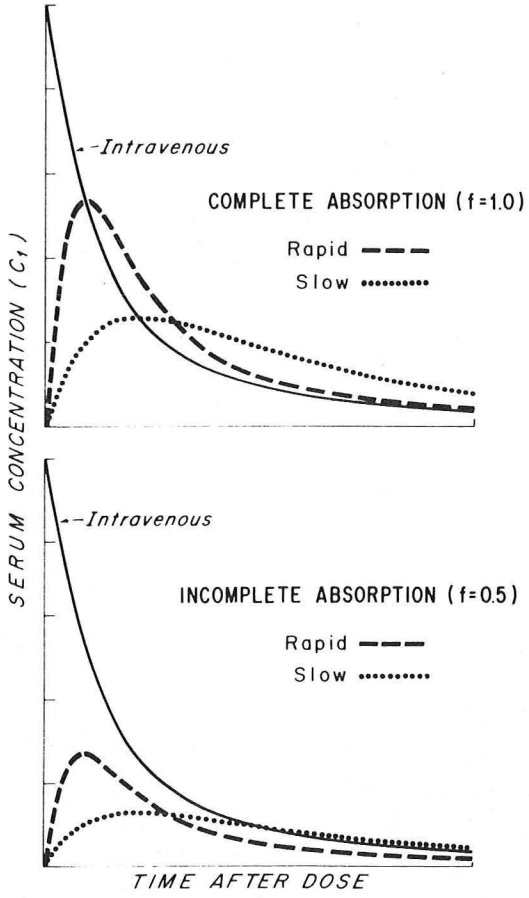
Figure 1: General schema relating dose of a drug to its effect

The pharmacologic role of the kidney can be analyzed with respect to each of the determinants indicated in the schema, but one must be aware that changes of the relationship between dose and response can occur by permutations of any one or, probably more likely, a combination of the determinants noted.

III. Determinants of the Relationship Between Dose and Concentration of a Drug in Blood

A. Absorption

Changes in absorption can occur by affecting rate and/or extent of absorption as illustrated in Figure 2. The rate of absorption determines the time at which, and magnitude of, peak concentrations of drug reached in blood. The extent of absorption determines how much of the drug enters the system and, consequently, the magnitude of the concentration of drug in blood.



Serum Drug Concentrations after Administration into Sites from Which Absorption Occurs with Varying Rates and Completeness.

Figure 2: Hypothetical absorption profiles

The majority of intestinal drug absorption occurs in the proximal small bowel. Some drugs can be absorbed in the stomach but even these drugs have the greatest component of their absorption in the small intestine. The rate of absorption, for the most part, then, is determined by the rapidity with which the stomach empties the drug to absorption sites. Consequently, diseases or other drugs which delay gastric emptying delay the time at which peak concentrations of drug occur. This rate of absorption can also be modulated by a variety of other factors such as physico-chemical complexing of the drug with other substances in the gastrointestinal tract, etc. However, these other factors, some of which are listed in Table 2, tend to have their greatest effect on the extent of absorption.

1. Factors concerning the drug
   a) Molecular weight
   b) Lipophilicity (e.g. oil:water partition coefficient)
   c) pK_a
   d) Drug metabolism by gut enzymes (e.g. non-specific esterases, dopa decarboxylase, monoamine oxidase)
   e) Drug metabolism by gut bacteria
2. Factors concerning the drug product
   a) Disintegration time (tablets)
   b) Dissolution rate
   c) Excipients and adjuvants
3. Factors concerning the patient
   a) pH of intestinal epithelium
   b) Gastric hydrochloric acid
   c) Rate of gastric emptying
   d) Intestinal motility (transit time)
   e) Surface area available for absorption
   f) Gastrointestinal disease
   g) Interaction with other drugs, ions in gut
   h) Presence of food (e.g. large meal) in gut

Table 2: Factors which can affect drug absorption

Intestinal motility is another factor that can affect the extent of absorption of slowly absorbed drugs such as guanethidine, bishydroxycoumarol, and some preparations of digoxin. Rapid transit allows less time for and causes incomplete absorption. This reduced absorption can be corrected by decreasing transit time.

The effects of renal dysfunction on rate or extent of gastrointestinal absorption have not been examined. However, one might speculate that uremia, 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. Thus, it behooves the astute clinician to be cognizant of these possibilities 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 the benzodiazepines precipitate in muscle and, consequently, are absorbed eratically 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 protocol: 1) this section will include effects

on distribution which change the concentration of drug in blood and 2) 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.

This separation is somewhat artificial for several reasons, the foremost of which is the fact that very little is understood about changes in distribution. 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. The mechanism of these effects, their consequences, and clinical relevance are poorly defined. I do not purport to understand the phenomena but have chosen a way to categorize effects on distribution which is easy to think about in terms of clinical importance. It is clear that 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. It is equally clear that 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 distribution. 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. Needless to say, further elucidation of this entire area is needed, but as clinicians, we must attempt to apply some modicum of logic to sorting out the known data and apply it to patient care. The categorization described above is my attempt to do so.

It appears with one exception that one needs to be concerned about changes in distribution only with drugs that are highly protein bound (~90% or more of the drug normally being bound to albumin). A list of such drugs would include penicillin, sulfonamides, thiazide and loop diuretics, sulfonylureas, etc., but no clinically important changes in distribution have been reported with these drugs. Potentially important distribution-related effects have been described with phenytoin, coumadin, salicylates, thiopental, and diazoxide. Phenytoin and coumadin represent drugs in which effects on distribution cause a change in the concentration of drug in blood. With the latter drugs, 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 and coumadin are displaced from albumin increasing the amount of drug free in plasma. This phenomenon is shown in Figure 3.

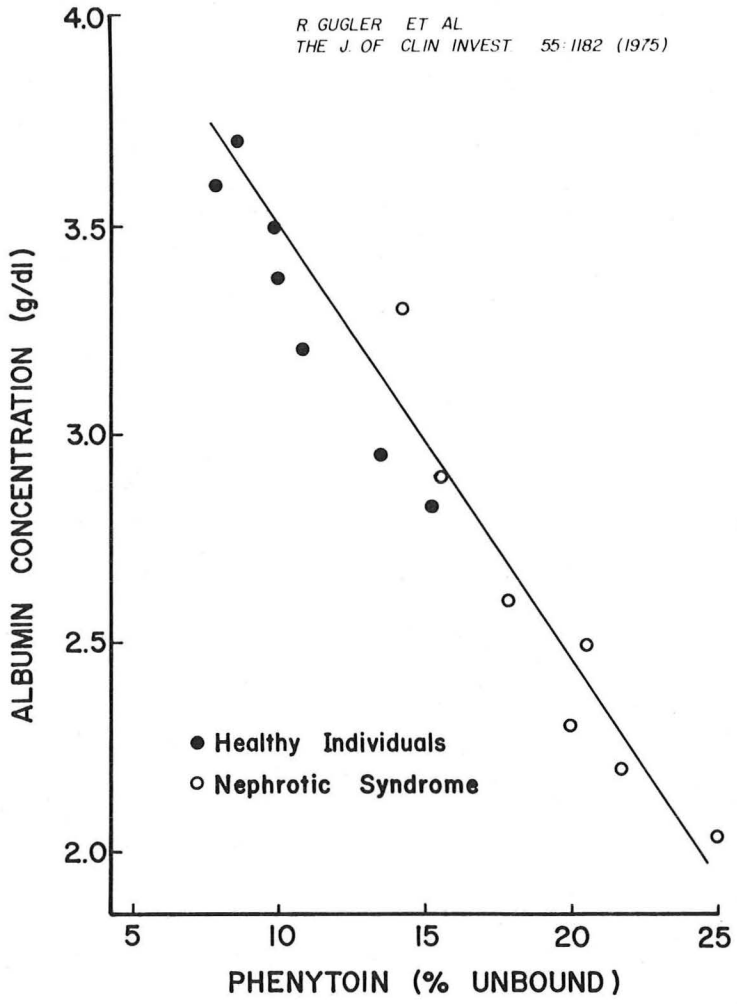


Figure 3: Relationship between serum albumin concentration and bound fraction of phenytoin

This displacement from binding in itself should cause an increased effect of the drug 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 tissues 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 sequence is illustrated schematically for phenytoin in Figure 4.

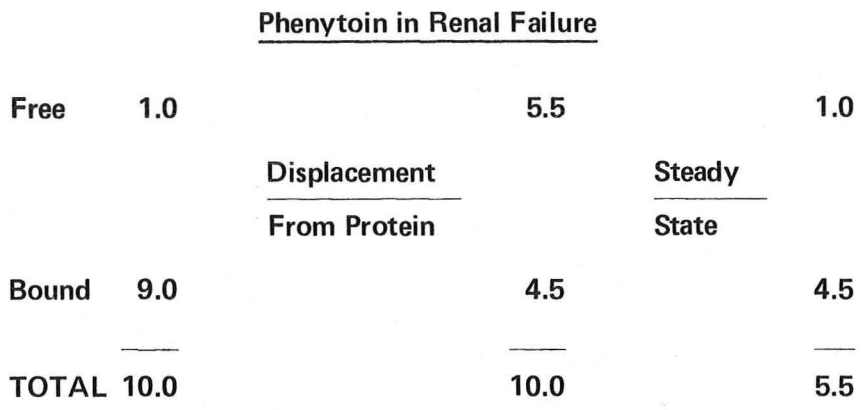


Figure 4: Schematic representation of the influence of uremia or hypoalbuminemia on the disposition of phenytoin

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 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.

Digoxin is the exception noted previously to the general rule that distribution changes pertain to highly protein bound drugs. In end-stage renal failure, the volume of distribution is decreased and a smaller loading dose of digoxin is needed to achieve a given concentration in blood. Therefore, the reduced maintenance dose of digoxin required in end-stage renal disease relates mainly to decreased ability of the kidney to eliminate digoxin, while additionally the drug distributes into a smaller volume so that a smaller loading dose is necessary. The effect does not alter the relationship between concentration in blood and effect.

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 inconsequential. The proximal tubule can metabolize morphine, dihydroxybenzene, 5-hydroxytryptamine,

and insulin but in amounts that are not clinically important.

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. Procainamide was cited previously as an example of the importance of this phenomenon. The oral sulfonylureas, excluding tolbutamide, are also converted to active metabolites which accumulate in uremia, potentially causing prolonged and long-lasting hypoglycemia. Meperidine is metabolized to nor-meperidine which depends on the kidney for elimination. Accumulation of the metabolite of meperidine can result in seizures. Oxypurinol, the active metabolite of allopurinol also accumulates in uremia though the clinical importance is unclear.

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 of drugs 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 shown in Figure 5.

Filtration

Protein Binding
Molecular Size
Glomerular Integrity
- **Decreased filtering nephrons**
- **"Leaky" glomerulus**

Figure 5: Determinants of the capacity for glomerular filtration of a drug

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

The 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 (~70,000) is selectively retained because it cannot be filtered. Consequently, these preparations remain in patients for weeks. Other drugs are small enough that there are no size limitations to filtration.

The integrity of the glomerulus as a seive is disrupted in nephrotic syndrome. Hypoalbuminemia results in decreased binding of a variety of drugs as discussed previously. In addition, 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 to be important compared to overall elimination.

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. Periodic reviews and compilations of drugs needing dose changes when GFR is decreased regularly appear in journals and bookstores. Because of the general awareness of the importance of glomerular filtration rate to the elimination of a number of drugs and because of the comparative lack of awareness of other important modes of renal handling of drugs, this discussion will deemphasize this former aspect of renal pharmacology. This is intended in no way to give short shrift to such an important area, but merely to elevate other aspects of renal pharmacology to equal importance and to equal cognizance in clinical settings.

A number of different approaches have been taken in coping with the burgeoning literature regarding the effects of changes in GFR and drug excretion. Bennett, and co-workers, for example, publish an updated series of tables every two years listing a large number of drugs with recommendations for dose adjustment when indicated. Dettli has devised a complicated system using rate constants (essentially reciprocals of half-life) which, probably because of its emphasis on mathematics, is shunned by clinicians despite its being as valid an approach as any of the others in the literature. Anderson, et al, have also published guidelines in a book, the abridged version of which is a chapter in Brenner and Rector's nephrology text. All or any of these sources are good and convenient sources of information. However, each has the potentially serious flaw of being too "cook book" in that insufficient emphasis is placed on the extent of interindividual variability or the important problem of changing renal function in an ill patient; additionally, one cannot assess the quality and, therefore, validity of the studies from which the data were derived if one uses these compendia as a sole source of information. Though each is referenced, the bibliography are not complete.

How should one use such sources in view of these problems? Interindividual variability mandates that therapy be tailored to each individual patient. Consequently, one must assume from the outset that guidelines from these general sources are starting points and that the individual patient must be closely monitored for end points of efficacy and toxicity. These end points include not only measurements of drug concentrations but, more importantly, clinical assessment of the patient. It is likely that

with close scrutiny one will need to adjust the dose in an individual patient differently from suggestions in general guidelines. For example, Noone recently described a large series of uremic patients in whom blood concentrations of gentamicin were closely monitored. They found that none of the many gentamicin guidelines or nomograms predicted the appropriate dose adjustment for any patient. One should also attempt to assess the specific medical literature relating to the particular drugs of concern in his patient(s). In this way, the clinician can better evaluate the quality of the data, thereby how it applies or does not apply to his individual patient, and most importantly gain a better understanding of the pathophysiology involved for use as a framework in approaching dose adjustment in individual patients.

I recommend a little known but excellent reference by Pagliaro and Benet which fills some of the gaps in the previously cited works. This compendium does not provide specific guidelines, but instead informs the user of the general effect of changes in renal and/or hepatic function on handling of a variety of drugs. Most importantly, this reference contains an extensive bibliography which can and should be used to extrapolate from the qualitative guidelines of the table to quantitative decisions in patients.

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 the example shown in Figure 6 in which iodipamide (a cholecystographic agent) induced a marked uricosuria in four patients studied by

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

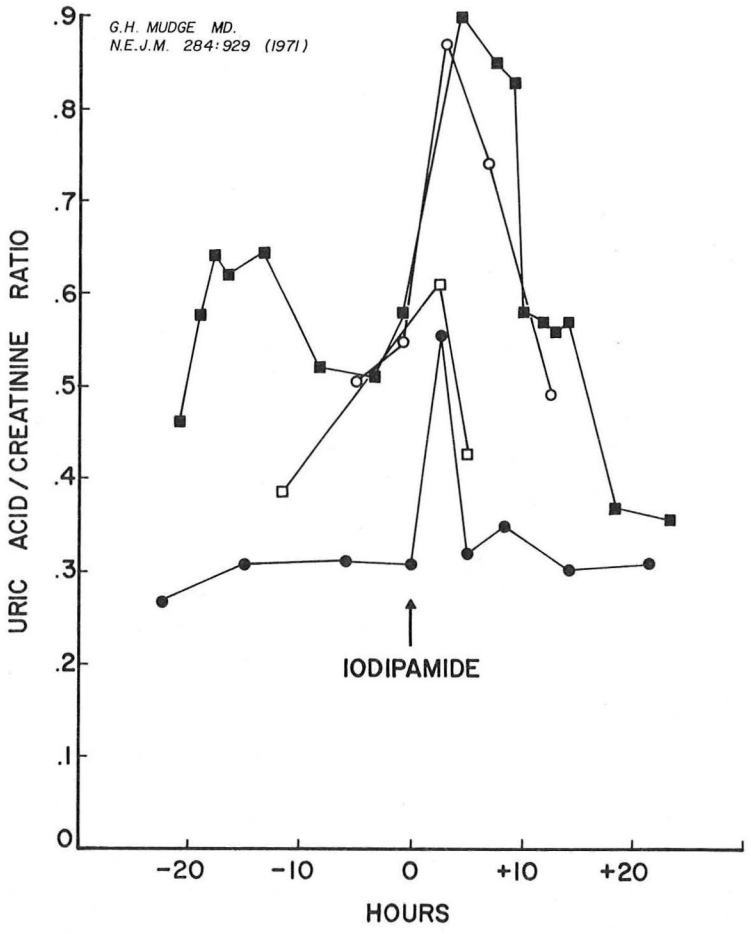


Figure 6: Effect of iodipamide on renal excretion of uric acid

The pars recta (straight segment) of the proximal tubule actively secretes into the tubular lumen a variety of organic acids and bases. The transport system for acids is more fully characterized than is that for bases, although our understanding of even the organic acid transport system is fragmentary.

The sine qua non of an actively secreted drug is a renal excretion rate greater than GFR. However, drugs with excretion rates less than GFR may also be actively secreted if the secretory capacity is low or if a portion of the secreted drug is reabsorbed more distally in the tubule. Active secretion has been studied by several techniques. Cross and Taggart originally described the method of incubation of slices of renal cortex in a medium containing the test drug. Active uptake of the drug resulted in a ratio of drug in the slice compared to that in the medium (S/M ratio) of greater than unity. Affirmation of an active process required that the S/M ratio return to or toward unity if the incubate included metabolic inhibitors. This technique is now considered a classic pharmacologic method for assessing and characterizing active transport. More sophisticated techniques like stop-flow, micropuncture, and micro-perfusion of isolated segments of renal tubule have been used recently to characterize these transport systems more fully. Unfortunately, it has been impossible to use the latter two methods to their utmost in probing active drug transport because very few drug analogs are available with specific radioactivity high enough to be studied in these preparations. Increasing our understanding of these pathways will require

further evolution of our methodology. The need for such understanding in addition to its pharmacologic importance is apparent from an intriguing observation by Grantham et al, that active secretion of organic acids into the lumen of the proximal tubule is accompanied by a parallel movement of considerable amounts of solute. Could this solute movement be important in overall volume homeostasis? No one knows.

In vivo methods used to study active transport include clearance studies in animals with a few such studies in man. These types of studies derive drug excretion rates, demonstrate saturability of the transport process, and show modulation of transport by metabolic substrates verifying and quantifying in vivo the same phenomena described in vitro.

Active secretion of drugs by the kidney is usually considered in terms of those compounds that are organic acids and those that are organic 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 elimination which can be competed for by spironolactone. Some patients coadministered these two drugs may need less digoxin. The site of digoxin transport in the kidney appears to be the distal nephron.

1) Organic Acid Transport

Table 3 shows a list of organic acids with potentially important renal secretion. Para-aminohippurate's transport is so avid that this compound

is used to measure renal blood flow; this is possible because at concentrations in blood less than the transport maximum, the kidney filters and secretes all of the p-aminohippurate in the blood perfusing the kidney.

Actively Transported Organic Acids
p-Aminohippurate
Salicylate
Probenecid
Indomethacin
Phenylbutazone
Penicillins
Sulfonamides
Thiazide Diuretics
"Loop" Diuretics
Methotrexate

Table 3: Organic acids actively transported in the kidney

As noted above, 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 prolonged concentrations of penicillin in blood. In fact, probenecid was discovered in 1951 by a systematic search for a compound that would inhibit the renal secretion of penicillin. Research had

demonstrated the active secretory component of penicillin's elimination so compounds were specifically sought that would block this secretion. Probenecid was found, eliminating the need to save patient's urine for extraction and reuse of the penicillin.

The effect of probenecid on the concentration in blood of cefamandole is shown in Figure 7 and a similar effect on furosemide is shown in Figure 8.

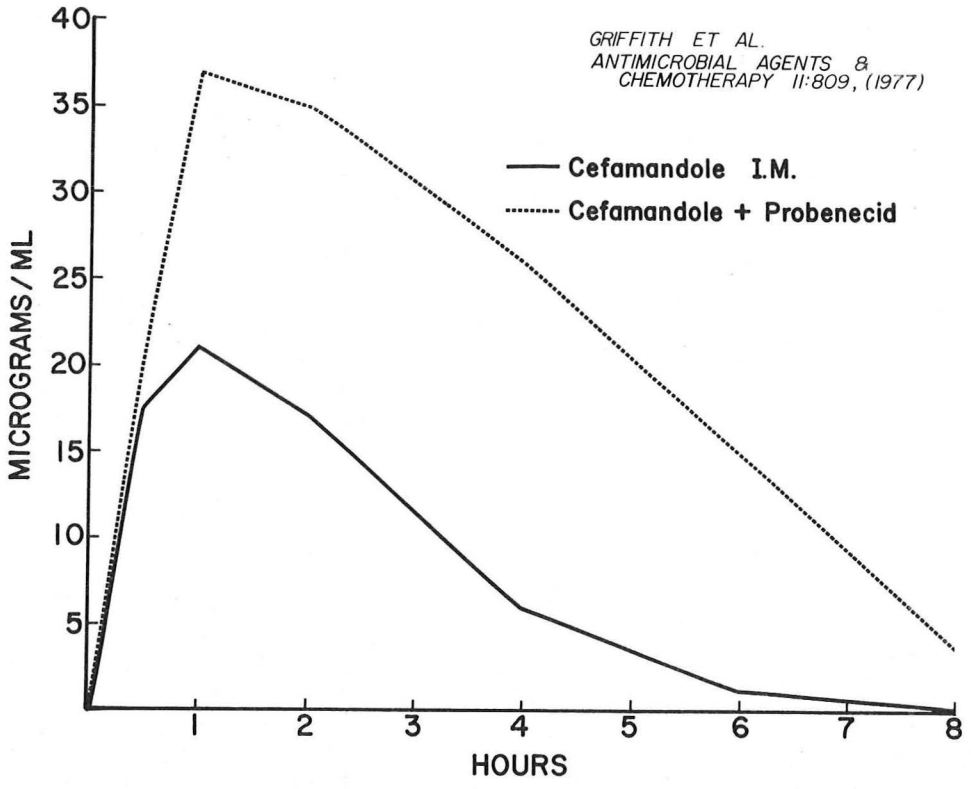


Figure 7: Effect of probenecid on the serum concentrations of cefamandole

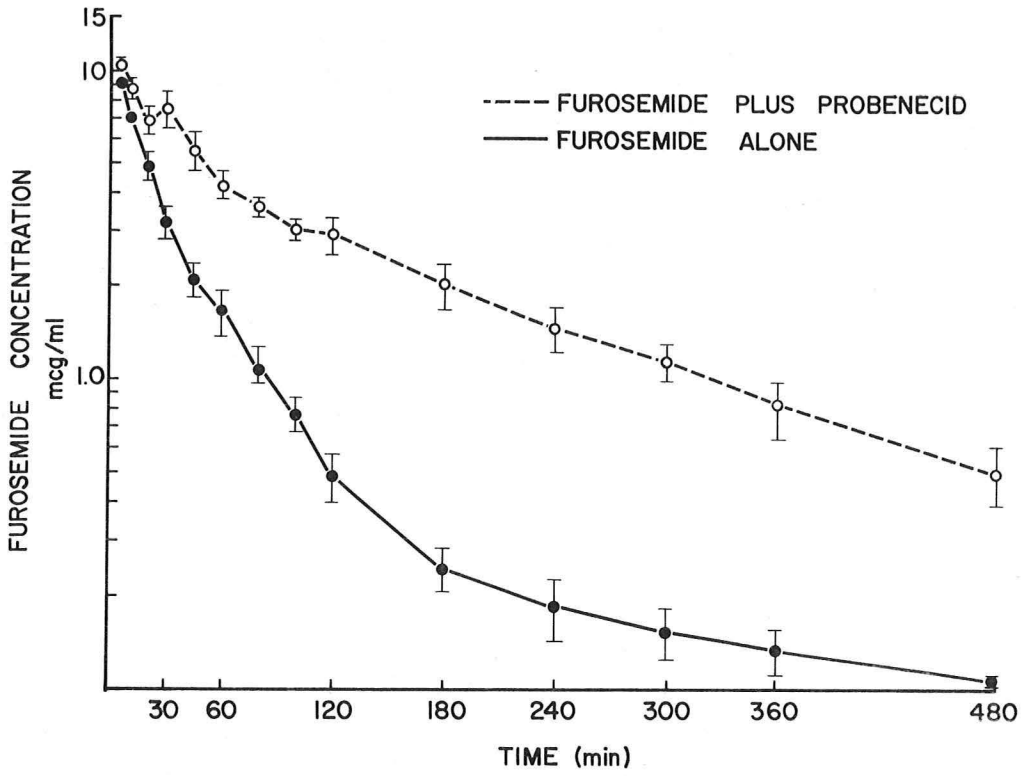


Figure 8: Effect of probenecid on the serum concentrations of furosemide

In both cases probenecid causes greater and more prolonged concentrations of the other drug in blood. This effect of probenecid may last for 12 hours or more, since probenecid or its active metabolites may "bind" to the transport mechanism and elute slowly.

All of the drugs listed in Table 3 have the potential to compete with each other. However, the degree to which they will compete is impossible to predict as illustrated in Figure 9 which shows the spectrum of effect by a variety of organic acids on the elimination half-life of penicillin.

DRUG	BEFORE DRUG	AFTER DRUG
Probenecid	40.4 ± 17.9	104.3 ± 46.0
Phenylbutazone	42.8 ± 14.4	102.2 ± 63.0
Sulfinpyrazone	42.6 ± 10.2	70.3 ± 15.8
Acetylsalicylic acid	44.5 ± 15.8	72.4 ± 35.9
Sulfaphenazole	34.9 ± 7.3	50.4 ± 14.9
Indomethacin	42.7 ± 17.5	52.2 ± 18.8
Chlorothiazide	53.5 ± 15.6	62.3 ± 12.0
Sulfamethizole	58.6 ± 13.8	70.6 ± 21.7
Sulfamethoxypyridazine	60.0 ± 26.3	50.8 ± 14.2

Figure 9: Effect of a variety of organic acids on the serum half-life of penicillin

Competition for secretion can be important clinically. The use of the probenecid-penicillin combination for gonorrhea has been discussed. Most clinicians are aware of the need to decrease the dose of methotrexate if probenecid is coadministered. Few are aware, with potentially disastrous consequences, of a possible similar need if other drugs listed in Table 3 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 Table 3.

Another clinically important example of the competition for transport is that which occurs between the accumulated endogenous organic acids of uremia and a variety of drugs. In fact, this mechanism is probably more important in mild to moderate renal failure than is decreased nephron mass in the decreased elimination of a number of organic acids and in the requirement for larger doses of organic acid diuretics 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. Table 4 lists bases which have been shown to undergo active secretion.

TETRAETHYLAMMONIUM
N – METHYLNICOTINAMIDE
MECAMYLAMINE
PROCAINAMIDE
QUINACRINE
ETHAMBUTOL

Table 4: Organic bases actively transported in the kidney

N-methylnicotinamide and tetraethylammonium are transported so avidly that they can be used similarly to p-aminohippurate to measure renal blood flow. 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 show cross-competition. For example, gentamicin is a base and has a high S/M ratio in renal cortical slices that decreases with metabolic inhibitors in the incubate. None of the aforementioned bases inhibit gentamicin uptake. Similar findings have been reported with other experimental compounds.

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 obviously 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 non-ionic 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 versus unionized drug can determine the extent of reabsorption. The net result is stated in Figure 10.

pH Dependent Kinetics

Weak Acid: As the pH increases, the ionized component increases, and excretion increases.

Weak Base: As the pH increases, the ionized component decreases, and excretion decreases.

Figure 10: Effect of urine pH on reabsorption of weak acids and weak bases

The relationship for weak acids of a drug's pKa and urinary pH is derived in Figure 11 and that for weak bases is derived in Figure 12.

WEAK ACIDS

$$HA \rightarrow H^+ + A^-$$

$$Ka = \frac{(H^+)\ (A^-)}{(H\ A)}$$

$$-\log Ka = pKa = -\log (H^+) - \log \frac{(A^-)}{(HA)}$$

OR $$pKa = pH - \log \frac{(A^-)}{(HA)}$$

OR $$pH - pKa = \log \frac{(A^-)}{(HA)} = \log \frac{\text{IONIZED}}{\text{UNIONIZED}}$$

THEREFORE, FOR A WEAK ACID, AS pH DECREASES, THE CONCENTRATION OF UNIONIZED DRUG INCREASES.

Figure 11: Derivation of the relationship between pH and the amount of unionized versus ionized species for organic acids.

WEAK BASES

$$BH^+ \rightarrow B + H^+$$

$$Ka = \frac{(B)\ (H^+)}{(BH^+)}$$

$$-\log Ka = pKa - \log (H^+) - \log \frac{(B)}{(BH^+)}$$

OR $$pKa = pH - \log \frac{(B)}{(BH^+)}$$

OR $$pH - pKa = \log \frac{(B)}{(BH^+)} = \log \frac{\text{UNIONIZED}}{\text{IONIZED}}$$

THEREFORE, FOR A WEAK BASE, AS pH RISES, THE CONCENTRATION OF UNIONIZED CONGENER INCREASES

Figure 12: Derivation of the relationship between pH and the amount of unionized versus ionized species for organic bases.

This relationship with two clinically used drugs is shown schematically in Figure 13 for quinine (a weak base) and probenecid (a weak acid).

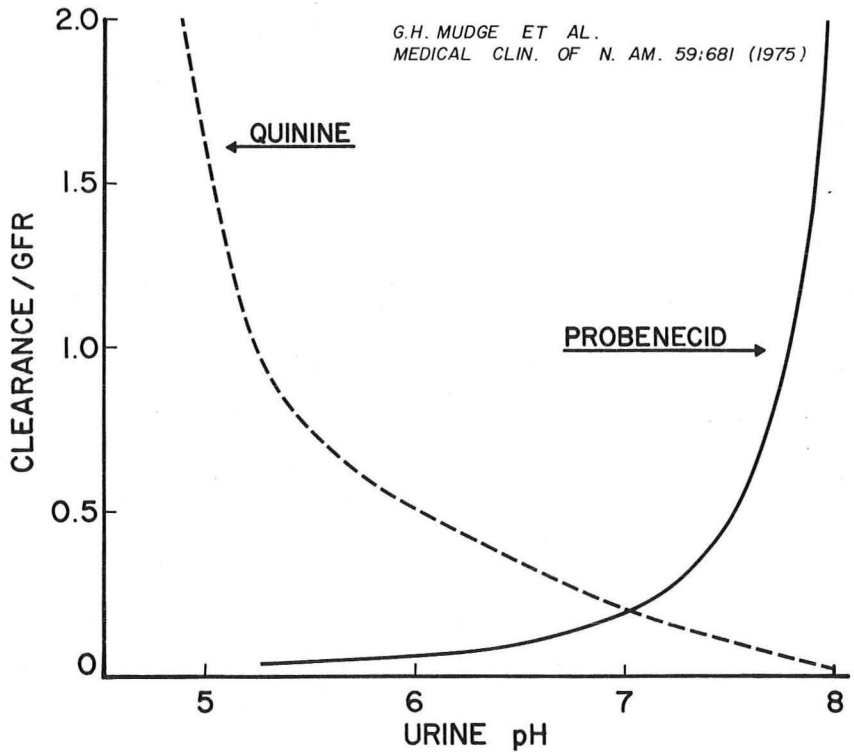


Figure 13: Effect of pH on the renal excretion of an exemplary weak acid and a weak base

Not all weak acids and weak bases demonstrate urine pH dependent elimination, so one cannot assume that these principles will apply to all weak acids and bases. Part of the lack of effect with some drugs probably 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. The importance of lipid solubility is demonstrated graphically in Figure 14.

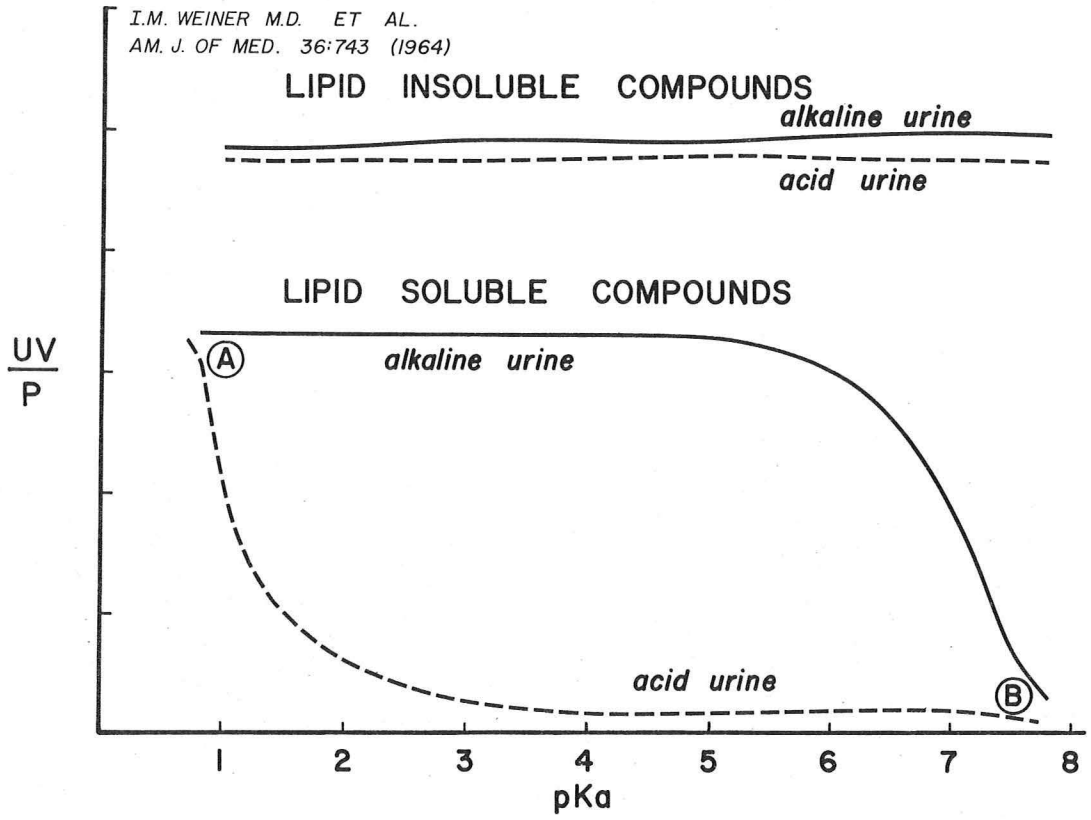


Figure 14: Effect of lipid solubility on urine pH-dependent elimination

Another modulator of the ability of the non-ionized congener's ability to pass across the lipid membrane may be antidiuretic hormone. In a series of elegant studies, Hayes et al showed in vitro that antidiuretic hormone can increase by 50-100% the ability of lipophilic compounds to pass across the toad urinary bladder, a structure functionally analagous to the mammalial collecting duct. These findings have not been extrapolated to man.

Other modulators of the effects of urinary pH on drug reabsorption are less well defined. Urinary pH has been shown to be an important determinant of elimination for the drugs shown in Table 5.

WEAK ACIDS:
SULFA DERIVATIVES
SALICYLATES
PHENOBARBITAL
WEAK BASES:
AMPHETAMINE
EPHEDRINE
PSEUDOEPHEDRINE
PHENCYCLIDINE (PCP)
QUININE
TOCAINIDE
TRICYCLIC ANTIDEPRESSANTS

Table 5: Compounds with clinically important urine pH-dependent elimination

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 Levy, et al, 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 the antiinflammatory effect of salicylates.

The effect of urinary pH on the elimination of amphetamine may be more well known 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. The effect of urinary pH on renal elimination of amphetamine is shown in Figure 15.

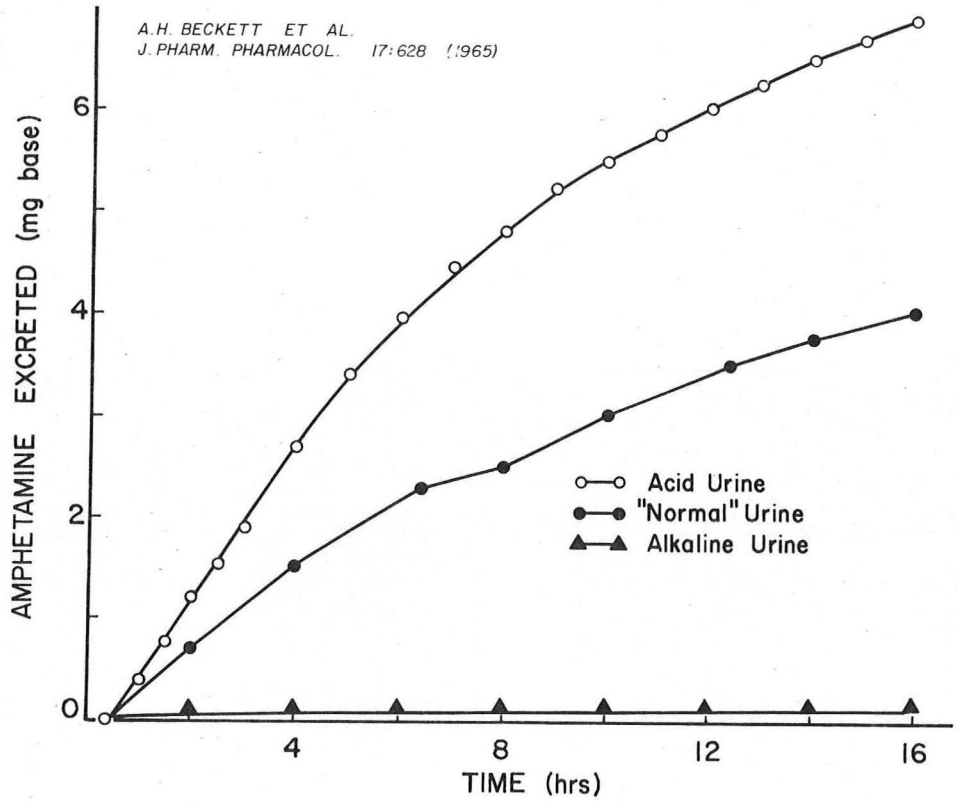


Figure 15: Effect of urinary pH on renal excretion of amphetamine

Recently, a similar importance of urinary pH has been demonstrated with phencylclidine (PCP, "angel dust", etc.), the abuse of which in some areas is at epidemic proportions. Toxicity can last for days and it has been shown that acidification of the urine can increase excretion and shorten the period of toxicity.

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 reabsorption of the drug.

A similar phenomenon is shown in Figure 16 where the administration of bicarbonate decreased the elimination rate of tocainide, an orally available lidocaine-like agent.

Renal clearance (ml/min) of tocainide in normal subjects

Subject	*No pretreatment or NH_4Cl (mean ± SD)*	*$NaHCO_3$ treated*
A. E.	63.3 ± 13.7 (n = 5)	12.8
E. W.	52.2 ± 23.5 (n = 6)	8.4
D. L.	73.7 ± 20.4 (n = 6)	17.5
L. V.	70.0 (n = 2)	—
H. J. A.	47.0 (n = 2)	—
R. M.	44.4 ± 17.2 (n = 5)	11.5
Overall mean ± SD	58.8 ± 11.4	12.6 ± 3.8

n: number of experiments conducted in a specific subject.

Figure 16: Effect of bicarbonate administration on renal excretion of tocainide

It is important to recall that a patient's freshly voided urine should usually be acidic. Persistent alkalinuria is abnormal and should be worked up. Though virtually every patient admitted to the hospital has a urinalysis performed with a dipstick pH determination, the value is often recorded but paid little attention. Urinary pH measurement can be important and should be given appropriate thought and analysis. To further emphasize this point, Figure 17 lists "iatrogenic" determinants of urine pH of which clinicians should be aware. These are, of course, only additional to and not exclusive of a variety of pathophysiologic modulators of urine pH.

Iatrogenic Acid-Base Disorders

Alkaline Urine
- **Bicarbonate containing antacids**
- **Alkalinization for stones**

Renal tubular acidosis
- **Outdated tetracycline**
- **Acetazolamide**
- **Amphotericin B**
- **Mafenide acetate**

Acid Urine
- **Acidification with bacteriostatics**
- **Potassium Depletion**

Figure 17: List of "iatrogenic" determinants of urinary pH

2) Urine Flow Rate

Urine flow rate can affect excretion of some drugs by two proposed mechanisms: 1) by decreasing the concentration gradient for reabsorption because the urine is dilute and 2) by decreasing the time for drug to diffuse out of the urine.

Urine flow rate has been shown to be an important determinant of elimination for the drugs shown in Table 6.

Excretion Affected by Urine Flow

Theophylline

Phenobarbital

Chloramphenicol

Table 6: Drugs with renal excretion affected by urinary flow rate

Figure 18 shows this effect of urinary flow on the excretion of theophylline in four subjects:

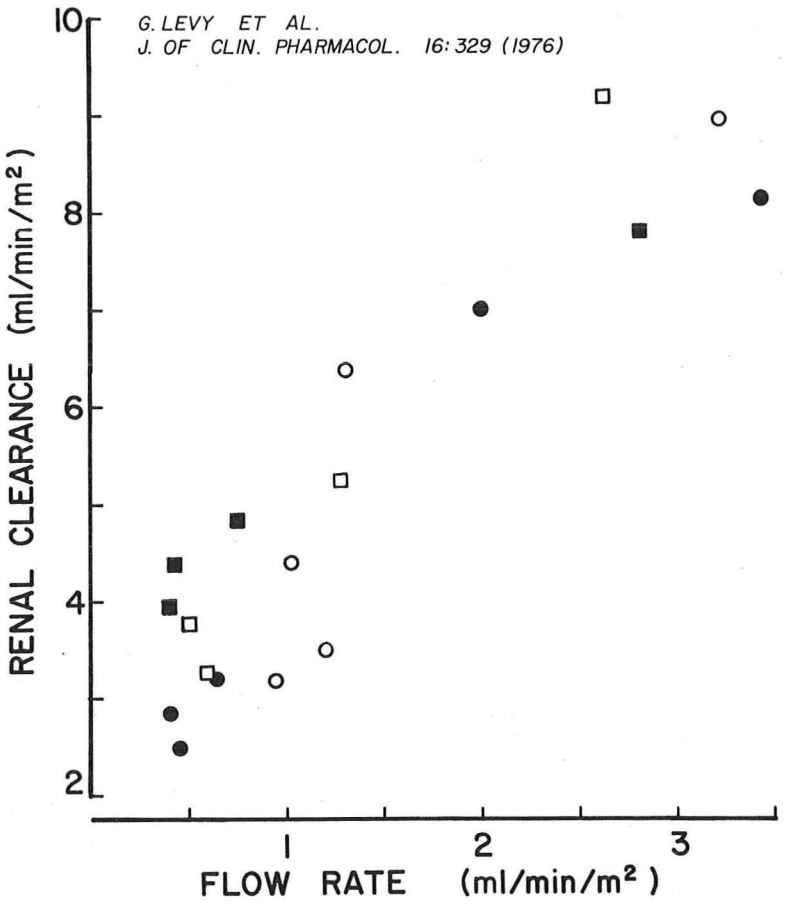


Figure 18: Effect of urinary flow rate on renal excretion of theophylline

This phenomenon would probably be clinically important only in patients with high urinary flow rates for prolonged periods of time.

The flow rate may be more important than inducing an alkaline urine in enhancing elimination of phenobarbital though one should not rely on forced diuresis alone and should clearly attempt to alkalinize the urine.

Clinicians seem to pay little attention to the importance of urinary pH and flow rate except in the case of salicylate or barbiturate 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 permit a detailed discussion of the elimination of drugs by dialysis, but it is important to briefly review some of the more pertinent determinants of a drug's dialyzability.

Molecular size can be an important determinant of dialyzability. In general, the influence of molecular size is that molecules of molecular weight less than 500 Daltons have flow dependent dialyzability, while elimination of those larger depends on surface area. For example, 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 membrance 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 discussed subsequently.

For a drug to be dialyzable, it must be water soluble (this does not apply to resin hemoperfusion which will be discussed subsequently). Glutethimide, though of small molecular weight, is insoluble in water and is not dialyzable. Drugs tightly bound to serum proteins, like propranolol, are poorly dialyzable.

The importance of dialysis relates also to a drug's intrinsic plasma clearance; namely, how fast the body can get rid of the drug exclusive of dialysis. For dialysis to be important therapeutically, clearance by dialysis must add an important increment to the intrinsic clearance; i.e., to be important dialysis should increase clearance by approximately 30%. Some general guidelines can be derived 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

$$Cl = 0.693\ Vd/t_{\frac{1}{2}}$$

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, that 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.

Similarly, if the half-life is short, 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 gentamicin is an example that illustrates the validity of this concept. In a patient with normal renal function the half-life of gentamicin is relatively short

(several hours). Therefore, clearance is large and dialyzing such a patient would not remove important amounts of gentamicin. However, gentamicin has a long half-life 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.

The considerations discussed above can help the clinician understand the factors determining dialyzability of drugs. How should he approach individual patients? Just as was discusssed with the influence of changes in GFR on elimination of drugs, there are several general references in the medical literature; however, the same precautions noted before should prevail. Namely, poor quality studies are used as a basis of some of the recommendations. For example, one of the many methodologic problems in this body of literature is the fact that there are several ways to calculate dialyzer clearance and many studies use the least accurate. Studies measuring dialyzer clearance by arterial-venous differences in drug concentrations and by blood flow rates through the dialyzer are suspect. A far more accurate method is to measure the amount of drug that comes out in the dialysate.

The clinician must also realize that individual variability cannot be overlooked and patients should be followed with determinations of drug concentrations in blood and with evaluation of clinical end points.

In overdose settings, it is also important that dialysis <u>not</u> be considered unless the literature clearly shows that dialysis of the toxin or drug is better than conservative management alone.

Recently, attempts have been made to increase the dialyzability of water insoluble drugs that are severely toxic in overdose settings; namely, glutethimide, methaqualone, and ethchlorvynol. 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 by resin hemoperfusion. Unfortunately, however, these drugs have large volumes of distribution so that the reduction in blood concentrations 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. The role of this mode of therapy is still unclear.

D. Dosing Interval

The frequency of drug administration and the amount of each dose determine the profile of drug concentration in blood over time as illustrated in Figure 19.

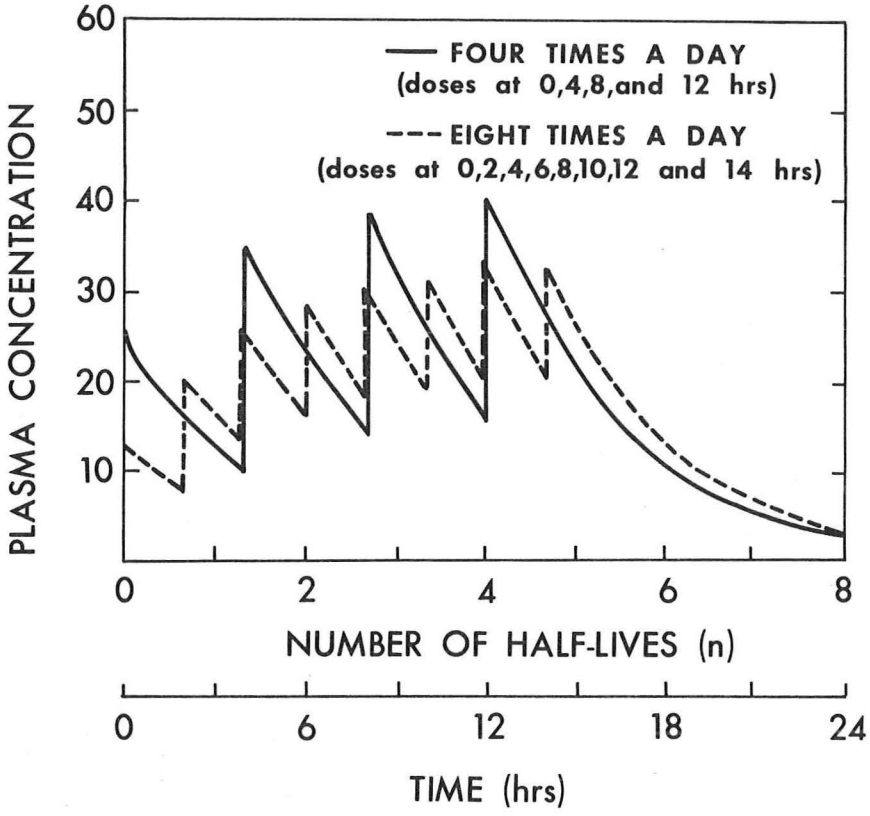


Figure 19: Effect of dosing frequency on blood concentrations of a drug

The figure shows that administering constant amounts of total drug but varying the intervals at which doses are given causes the average drug concentration attained in blood to be the same but the oscillation around the mean level to be different. Widely spaced intervals of dose administration cause wide swings from peak to trough drug concentrations compared to more frequently administered doses.

The importance of this concept as far as renal pharmacology is concerned is in the clinical setting of a changed capacity for renal elimination of a drug with a need to increase or decrease the total amount of drug administered. The usual case is a need to decrease the total amount of drug in a patient with decreased GFR. This decrease can be accomplished in two ways as shown in Figure 20.

Adjusting the Dosage Regimen

Variable dosage regimen: Decrease the amount administered with each dose; maintain the same dosing interval as in normal renal function.

Variable frequency regimen: Increase the interval between doses; maintain the amount administered with each dose the same as in normal renal function.

Figure 20: Options for decreasing the total amount of drug administered

It is difficult in perusing the medical literature to decide which approach is best. The dilemma is well illustrated with gentamicin or other aminoglycosides. There exist a variety of nomograms and formulae for adjusting the dosage regimen for gentamicin. The only controlled trial of the variable dose versus the variable frequency regimen was conducted at this institution and concluded that there was so much inter-individual variability that the two regimens could not be compared; namely, patients administered gentamicin designed to give them a blood concentration pattern like that of a variable frequency regimen often demonstrated a pattern more like that of a variable dosage regimen and vice versa. Consequently, in trying to decide which approach is best, one must try to piece together a number of different sources in the medical literature.

Proponents of the variable dosage regimen emphasize animal and human studies showing increased efficacy when concentrations of antibiotic are maintained within the therapeutic range at all times. Opponents of this regimen emphasize that the variable frequency regimen gives equal efficacy and less nephrotoxicity. The proponents counter with large series of patients they have managed which have a very low incidence of nephrotoxicity. The moral of this story is probably that good doctors take good care of their patients no matter which regimen they use. I personally feel that the variable dose regimen is preferable if the patient's renal function can be followed closely and the dose of gentamicin decreased at the first evidence of toxicity. I cannot and do not condemn the variable frequency regimen, and in many hospital settings this is probably a better regimen simply

because it is easier for the nursing staff to administer a constant dose of a drug rather than measuring out small, unfamiliar milligram amounts of the drug. I think clinicians should be aware, however, that if they use the variable frequency regimen, and the patient does not respond, that improvement may ensue with switching to a variable dosage regimen.

In Figure 21, I offer the "Chan Nomogram" as a starting point for dose adjustment following the variable dosage regimen.

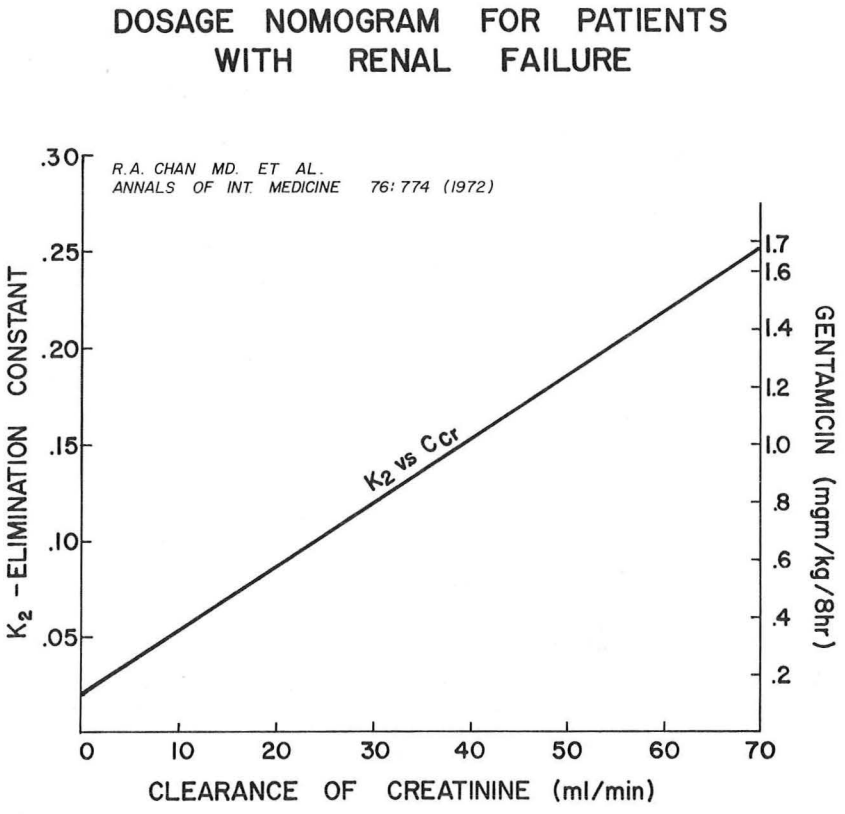


Figure 21: Nomogram for adjusting the dose of gentamicin depending on renal function using the variable dosage regimen

IV. 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 the drug concentration in blood were discussed previously. This section will consider 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. Figure 22 depicts the change in albumin binding of diazoxide that occurs with uremia and the resultant increased anti-hypertensive effect though the total concentration of diazoxide in blood remained the same as in non-uremic patients.

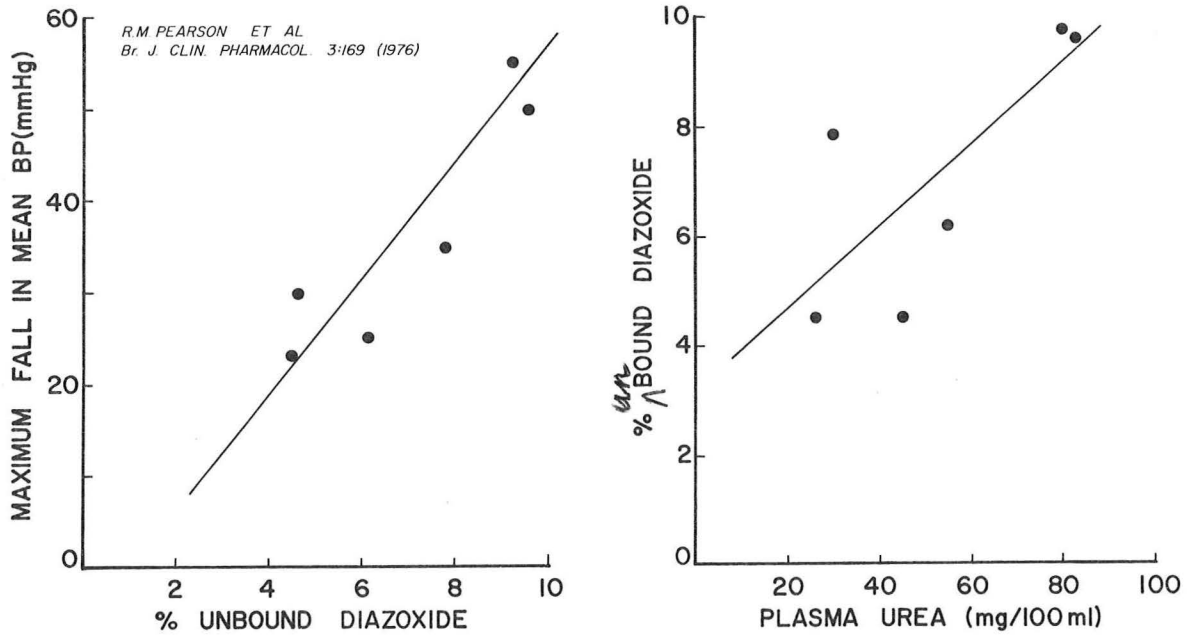


Figure 22: Relationship among uremia, protein binding of diazoxide, and antihypertensive effect

A similar phenomenon occurs with thiopental anesthesia as demonstrated in Figure 23. The dose needed for attaining a certain level of anesthesia was less in subjects after urea infusion, or, considered in another light, the same concentration of anesthetic caused more depression of consciousness in subjects administered urea than in normals.

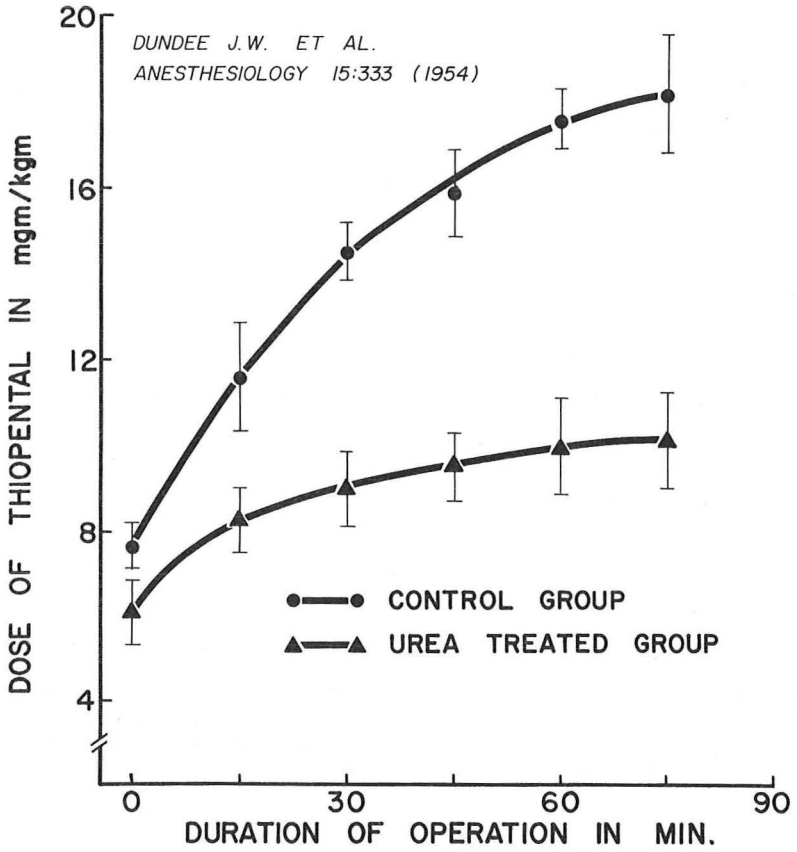


Figure 23: Effect of urea on duration of anesthesia and dose of thiopental

Changes in systemic pH can also affect distribution of a drug to a site of activity without changing concentrations in blood. Figure 24 lists the drugs for which evidence exists for such a phenomenon.

SALICYLATES
PHENOBARBITAL
MECAMYLAMINE

Figure 24: Drugs in which systemic pH affects distribution from blood to the site of action

Figure 25 shows the effect of acidemia on the distribution to tissues of salicylate.

TREATMENT	BLOOD pH	PLASMA	MUSCLE	BRAIN	LIVER
Sodium salicylate 400mg/kg I.P.	7.40-7.51	425±7	174±8	141±6	301±7
Sodium salicylate 400mg/kg plus sodium acetazolamide 25mg/kg I.P.	7.07-7.10	436±13	235±8	254±3	413±9

Figure 25: Effect of systemic acidemia on tissue distribution of salicylate

The same increased distribution into the central nervous system during acidemia occurs with phenobarbital. Central nervous system toxicity at any given blood concentration of either of these drugs is increased during acidemia without changing blood concentration. 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. It is obvious that an important part of therapy of salicylate or phenobarbital toxicity would be correction of a systemic acidemia.

A similar phenomenon occurs with mecamylamine, a weak base, the site of action of which is extracellular. Acidemia favors the ionized congener, increasing amounts of mecamylamine extracellularly at its site of action and increasing its hypotensive effect. This phenomenon has not been reported in man.

V. 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, phenothiazines, and tricyclic antidepressants. Alkalosis, 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 digoxin in blood and that at the active site. Whether the other conditions predisposing to digitalis toxicity represent true changes in sensitivity is unclear.

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 in addition follow clinical end points to assess response.

VI. Conclusion

The kidney can influence the disposition and resonse 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 function can affect handling of a drug in many different ways, the clinician must understand not only the pathophysiology of his patient's disease but also the pharmacology of the drugs being used to assess clinical end points of efficacy and toxicity as a guide to therapy.

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V. Conclusion