Drug Prescribing for Patients in Renal Failure

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Polypharmacy for nonrenal complications of chronic kidney failure is often a necessary part of the solution in clinical management, but it may also be part of a larger problem: drug toxicity. Since adverse drug reactions occur more frequently when renal function is impaired, the situation mandates sound clinical judgment, vigilant monitoring, and knowledgeable adjustment of drug regimens.

Most patients with chronic kidney failure have other, accompanying medical problems, not only hypertension and heart disease but anemia, osteodystrophy, and metabolic disturbances as well. Many of these nonrenal complications are not fully corrected by dialysis but may respond to pharmacologic therapy; in general, patients at all stages of chronic renal failure often are treated with a number of different drugs. Since most drugs in common use are excreted at least in part by the kidney, it is not surprising that adverse drug reactions occur more frequently when renal function is impaired.

A relationship between the presence of kidney disease and drug toxicity was first emphasized by J. W. Smith and associates, who showed that the incidence of adverse reactions increased from 9% when blood urea nitrogen was less than 20 mg/dl to 24% when the BUN exceeded 40 mg/dl. Smith and co-workers also established that the number of drugs administered per patient and the incidence of drug toxicity were related. Thus, hospitalized patients receiving fewer than five medications had a reaction rate of 4.2%, compared with 24% to 45% among those receiving 10 or more. An association between the number of medications taken and the frequency of side effects was subsequently confirmed by others through clinical observation and surveillance studies, and again, the presence of renal disease often made drug therapy a potentially hazardous undertaking.

However, despite the fairly extensive literature, not much information exists as to the actual prescribing practices of the physicians caring for this group of patients. To start a data base, we recently studied the drug regimens prescribed for patients with chronic renal failure who were on dialysis. According to our survey, which covered 1,023 patients at 27 dialysis units in nine states, the mean number of drugs per patient was 7.7, and 24% of the patients were treated with 10 or more drugs. When individual patient records were compared, there was no difference in the mean number of medications prescribed between men and women, or between patients who had had transplants and those who had not. The factors definitely associated with increased drug usage were patient age (over 30), duration of dialysis, and presence of underlying diabetic and hypertensive nephropathy.

Not unexpectedly, in this population receiving multiple pharmacologic agents, there was considerable frequency of drug duplication (12%), potential dosage error (9%), and potential drug interaction (15%). Drugs with relatively strong contraindications in patients with kidney disease (large doses of magnesium-containing compounds, tetracyclines, nitrofurantoin, ethacrynic acid, aldosterone antagonists) were prescribed in 2.5%. Perhaps the most striking observation was the degree of intercenter variability in medication use. The empirical nature of many aspects of

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Mechanisms of Adverse Drug Reactions in Kidney Disease

**PHARMACOKINETIC FACTORS**
- Decreased Hepatic Drug Metabolism
- Decreased Renal Drug Metabolism

**PHARMACODYNAMIC FACTORS**
- Decreased Drug Protein Binding
- Target Organ Alterations

Medical therapy for patients with chronic renal failure could account in part for these differences. For example, although controlled prospective studies indicate that 1,25-dihydroxyvitamin D and anabolic steroids can improve anemia and bone disease, respectively, in some dialysis patients, the precise indications for prescribing these agents are not established. Reflecting this uncertainty, the proportion of patients at individual centers receiving these treatments ranged widely—from 3% to 100% for anabolic steroids and from 0% to 76% for vitamin D preparations.

This tendency toward all-or-nothing therapy was also apparent for other medications. For example, oral iron was routinely administered to every patient at six centers, while at four units no patient received iron. This is difficult to reconcile with the fact that there are simple, objective ways to detect iron deficiency. A similar lack of individualization, although less marked, was noted for sodium bicarbonate, calcium salts, digitalis glycosides, and antiplatelet agents.

The practice of using many medications in renal failure patients appeared to relate not only to the presence of associated complications and disabilities but also to major differences in prescribing practices.

No attempt was made to determine whether the therapy given actually proved harmful or, indeed, whether the patients were taking the medications. However, it is clear from our knowledge of drugs and the kidney that some of the therapy prescribed may have been excessive and injurious. On the other hand, drugs are often necessary for a variety of reasons, and it would have been undesirable to withhold them. There is a middle ground, however, based on an understanding of the mechanisms that predispose to adverse drug reactions when the kidneys fail. This is particularly important in clinical situations in which multiple drugs are used to treat complications of renal disease. However, even then, there are practical guidelines to reasonably safe and effective drug therapy.

Since the kidney is the major excretory organ for many drugs, usual doses may need to be significantly reduced to avoid high blood levels and, thus, adverse reactions. In addition, physiologic and biochemical disturbances present in severe renal disease may alter extrarenal parameters, such as plasma protein binding or hepatic metabolism of drugs. Consequently, appropriate adjustments have to be made in maintenance dosage levels to prevent side effects.

**Pharmacokinetics and Pharmacodynamics**

The most basic relationship in pharmacokinetics is between the dose of drug given and the blood level that results; pharmacodynamic factors, in turn, account for the variation in response to a given plasma drug concentration. Both may be altered in renal failure, thereby predisposing to drug toxicity. The amount of the administered dose that ultimately reaches the circulation depends, first, on absorption and bioavailability. For orally administered drugs, the rate of drug transfer across the gastrointestinal mucosa is influenced by characteristics of the absorption site (blood flow, pH, contact time, surface area, presence of additional drugs) and physiochemical properties of the drug (molecular size and shape, water and lipid solubility).

Extensive data are not available
on the effect of renal failure on drug absorption. However, because multiple drugs are often administered and because numerous physiologic disturbances may alter gastrointestinal absorption, it behooves the clinician to be aware of potential bioavailability problems in patients with renal failure. For example, such patients are often treated with phosphorus-binding antacids, which decrease absorption of such drugs as ampicillin, digoxin, isoniazid, quinine, and sulfadiazines.

Of course, bioavailability of drugs also depends on the amount metabolized or inactivated by the liver before reaching the systemic circulation. This first-pass elimination may be a major determinant of the variation between patients. Propranolol has been used as the model drug in this regard. Normally 50% to 80% of an administered dose may be removed by the liver; however, in uremia bioavailability is substantially increased because of decreased first-pass elimination. In contrast, bioavailability of furosemide is generally reduced in renal failure by increased first-pass elimination. However, several factors influence this aspect of drug disposition; for instance, if there is portal-systemic shunting of blood or liver dysfunction, first-pass elimination of a given drug may be greater. (The rather complex relationships between compromised renal function and hepatic metabolism will be discussed later.)

Every drug has its own volume of distribution ($V_D$), which has been experimentally determined by giving a known intravenous dose to a patient population and measuring the resulting plasma levels. It should be noted that the $V_D$ value does not correspond to any single anatomic compartment; rather, it is a mathematical concept designed to relate the amount of drug in the body to a given plasma level. (The $V_D$ of a drug can be calculated by dividing the amount administered by the steady-state plasma concentration.) Generally, drugs that are highly lipid-soluble and therefore readily penetrate cells have high $V_D$ values. In contrast, drugs that are highly protein-bound often are restricted to a smaller distribution and thus have low $V_D$ values (e.g., for gentamicin, $V_D = 0.2$ L/kg). The $V_D$ value of a drug can be a useful aid in treating patients with renal disease. For instance, lipid-soluble drugs with high $V_D$ values (e.g., amitryptiline, $V_D = 10$ to 20 L/kg) tend to have long half-lives, and the high $V_D$ limits the availability of the drug for removal by dialysis. Other drugs with high $V_D$ values include digoxin (10 L/kg) and phenothiazines (7 to 9 L/kg).

Drug distribution, when altered by disease states, may change the pharmacologic response to a given agent or its elimination rate. In this regard, renal failure may substantially increase or decrease $V_D$. For example, it is higher for phenytoin and lower for digoxin. The reasons for the altered $V_D$ of drugs in renal failure relate in part to drug plasma protein binding, as well as to changes in total body water and the ratio of total body lipid to lean tissue mass. It is relevant that alterations in drug distribution, metabolism, and elimination occur as people age. For example, total body water decreases in the elderly, and therefore drug levels may increase. Lower plasma albumin concentrations, found frequently in the elderly and in patients with renal disease, also decrease protein binding and distribution of many drugs, since they normally bind mostly to albumin.

Once in the circulation, a drug's clinical action is dependent on the unbound fraction, the only portion available for diffusion out of the vascular system to sites of pharmacologic activity, biotransformation, and excretion. However, most methods of estimating the plasma concentration of a drug measure the total amount present, including both free and protein-bound drug. Therefore, a good relationship between plasma concentration and intensity of drug effect exists only if protein binding of the drug is constant. Renal failure alters the degree of binding of several drugs to plasma proteins. For unknown reasons, most of the drugs that exhibit decreased binding are acidic. Only one acidic drug studied to date—indomethacin—has demonstrated normal protein binding.

Several studies have offered evidence suggesting that "competitive displacers" may be present in uremia to alter protein binding: 1) A number of acid metabolites accumulate in renal failure, and as noted, protein binding of acidic drugs is primarily affected. 2) Charcoal treatment of serum of patients with renal failure may restore normal protein binding. 3) Decreased binding of drugs used in renal failure can be reversed by dialysis in some but not all patients. 4) Recently, inhibition of protein binding was demonstrated in experiments using a nonionic polystyrene-divinylbenzene copolymer resin to treat acidified uremic plasma. Although the resin markedly improved binding of phenytoin to plasma protein, an alcohol eluate produced a substance that when reconstituted with normal plasma caused a dose-dependent decrease in phenytoin and tryptophan protein binding. This inhibitor was water-soluble, heat-stable, and dialyzable.

In a second theory, renal failure is thought to induce either chemical or ultrastructural changes that
alter normal drug-binding sites on albumin. In fact, isoelectric focusing techniques in uremic patients have shown abnormalities in the B band of albumin that correlate with decreased protein binding of drugs.

It is difficult to evaluate the clinical significance of these alterations in protein binding. On the one hand, the increased amount of free drug in plasma should lead to a more intense pharmacologic effect. However, impaired binding may also accelerate total body clearance, since many drug elimination processes proceed at rates proportional to the level of free drug. In studies of patients who were nephrotic and hypoalbuminemic, an anticipated increase in free, or unbound, drug was observed. But this was balanced by an increase in VD values of the drugs studied and an increase in total clearance rates, so that absolute plasma concentrations were not higher after all. However, a number of studies demonstrate an increase in adverse drug reactions in a setting of diminished protein binding, hypoalbuminemia, or both.

This has been shown for phenytoin, prednisone, and benzodiazepines. Taken together, the evidence suggests caution in treating patients with renal or hepatic disease, who may be subject to enhanced pharmacologic effects of drugs at normal plasma concentrations by virtue of altered protein binding.

**Drug Metabolism**

Many drugs are biotransformed before being excreted. These processes occur predominantly in the liver and result in the formation of water-soluble, polar metabolites, which are more readily excreted. The first phase of hepatic metabolism is drug oxidation, followed by conjugation of the drug molecule to glucuronide, glycine, or sulfate (phase II). Drugs can also undergo reduction and hydrolysis in phase I and methylation and acetylation in phase II. Obviously, advanced liver disease substantially affects the metabolism of a number of drugs. The assumption had been that such hepatic biotransformations were not greatly affected by renal insufficiency or failure. But it has become increasingly apparent in recent years that renal failure per se can lead to abnormalities in the hepatic metabolism of some drugs. For example, in a rat model, renal insufficiency decreased specific activity of the hepatic mixed-function oxidation system, giving a biochemical explanation for delayed oxidation reactions. Conjugation, reduction, and hydrolysis reactions also may be slowed in uremia, and animal studies confirm abnormalities in the activity of the hepatic enzymes that modulate these reactions. However, hepatic biotransformations may also be accelerated in uremic patients, and the clinical significance of these changes remains to be elucidated. It is important to note, too, that some drugs are biotransformed to pharmacologically active metabolites, which, often more polar and water-soluble than the parent compound, may require intact renal function for prompt excretion. In severe renal failure, metabolites...
that usually exist in small quantities may cause problems if they accumulate.

Finally, although drug metabolism has been thought to occur predominantly in the liver, the kidney has been demonstrated in recent studies to be quite active metabolically. Renal biotransformation and metabolism may prove more important than hepatic activity for certain drugs. This is an important field, still in its infancy.

The microsomal fraction of several tissues contains an enzyme system that catalyzes the oxidation of many organic compounds. Up to now, this system has been best characterized in the liver. In brief, it consists of three components: a hemoprotein, cytochrome P-450; a membrane-bound flavoprotein, NADPH-cytochrome P-450 reductase, required to reduce cytochrome P-450 so that it can bind to oxygen; and a lipid, phosphatidylcholine, which appears to facilitate electron transport. It is evident that the kidney also exhibits mixed-function oxidase activity. This has been shown in several species, including humans. Various types of test compounds are biotransformed by the renal cytochrome P-450 oxidase system. The list includes fatty acids, aminopyrine, biphrenylaniline, and ethylmorphine. Except for hydroxylation of fatty acids, the quantitative contribution of the kidney to oxidation reactions appears less than that of the liver. How much the kidney contributes to oxidation of commonly used drugs, as compared with the liver, is not known. Present evidence localizes cytochrome P-450 in the kidney to the cortex.

Similarly, the kidney plays a part in biotransformation of organic agents by synthetic (conjugation) reactions, but its contribution to drug metabolism has not been worked out. The reaction products of this pathway include glucuronide, sulfate ester, and glutathione conjugates. Via the glucuronide pathway, chemicals are detoxified by transformation to highly polar compounds that are water-soluble. In a reaction catalyzed by uridine diphosphate glucuronoyl transferase. Current information suggests that there is wide species variation of this enzyme activity in the kidney. In some species the enzyme appears highly active in forming glucuronide conjugates.

The sulfate conjugation reaction transfers a sulfate group from 3'-phosphoadenosine-5'-phosphosulfate to acceptors of either phenolic acid, alcohol, or amine groups, with subsequent formation of 3'-phosphoadenosine-5'-phosphate and either a sulfate ester or sulfamate group. Sulfate conjugates are also highly polar, but unlike glucuronide conjugates, they often retain pharmacologic activity. Current evidence indicates that the kidney performs sulfate conjugation but in less quantity than the liver.

Glutathione conjugation is catalyzed by glutathione transferase, which is also present in the kidney. Glutathione transferase activity also appears to be much less important in the kidney than in the liver. However, glutathione conjugates are subsequently connected to δ-γ-glutamylcysteine derivatives by γ-glutamyltransferase, an enzyme that has high activity in renal tissue. A δ-substituted cysteine conjugate is then formed by a peptidase from the δ-γ-glutamylcysteine, and the final reaction is the formation of mercapturic acid by acetylation of the cysteine conjugate. This reaction is catalyzed by N-acetytransferase, also highly active in the kidney. Recent studies showed that these enzymes are localized predominantly in the proximal straight tubule.

As in the liver, glutathione conjugation in the kidney normally protects tissue from injury by electrophile carbon atoms. For example, if glutathione is so depleted in the kidney as to be unavailable for detoxifying acetaminophen, toxic drug metabolites form, causing renal pathology and necrosis. Also, as in the liver, such pathology can be prevented in experimental animals if they are pretreated with cysteine, a precursor of glutathione. Thus, vital renal macromolecules appear to be damaged when the glutathione pathway is depleted or oversaturated, preventing reactive acetaminophen metabolites from being detoxified.

Cephaloridine is an example of a drug that has a dose-dependent nephrotoxicity, expressed in pathologic changes affecting the proximal tubule brush border; progression to severe proximal tubular necrosis occurs with larger doses. Pretreatment of experimental animals with agents that inhibit the microsomal oxidase pathway of drug metabolism significantly diminishes (continued on page 153)
RENAL FAILURE (from page 149)

Tubular damage due to cephaloridine. Therefore, renal metabolism of the drug is required before serious pathology can result.

To sum up, in the presence of renal failure, hepatic metabolism of some drugs may be impaired. In addition, the kidney per se plays a role in drug metabolism. Because of these factors, one must be aware of prolonged drug half-life and drug accumulation when administering drugs to patients with diminished renal function.

Drug Handling by Kidney

Having discussed the problems of drug administration that are caused by a reduction in metabolic capacity in renal failure, we now address those related to impaired drug elimination. With most drugs in clinical use, elimination follows first-order kinetics; that is, the amount of drug eliminated per unit of time is proportional to the amount in the body. The rate of drug elimination is often expressed by its half-life (T1/2), the time required for the concentration of a drug to decline by 50%. The half-life values of drugs have been determined from measurements of plasma concentration after equilibration between plasma and tissue storage sites. For any drug, the amount remaining in the body after one, two, three, four, and five half-lives will be, respectively, 50%, 25%, 12.5%, 6.25%, and 3.13%. In other words, 97% of an administered dose is eliminated in five half-lives. Mathematically,

\[ T_{1/2} = \frac{0.693}{k_r + k_m} \]

where \( k_r \) is the renal elimination rate constant and \( k_m \) the nonrenal (metabolic) elimination rate constant determined by hepatic metabolism. It can be seen that half-life varies inversely with \( k_r \) for drugs excreted mainly by the kidney. Thus, in renal failure, as values for \( k_r \) decline, the half-life values increase.

The most obvious abnormality in patients with renal failure is decreased excretion of active, unchanged drug. If the dosage is not altered accordingly, the drug will accumulate, reaching toxic levels. Drugs in this category include aminoglycoside antibiotics, digoxin, penicillins, tetracyclines, methotrexate, and ethambutol. A majority of other drugs are probably biotransformed to metabolites, which then undergo renal excretion. Both renal and extrarenal factors influence the rate of drug excretion by the kidney. Several of the extrarenal factors have already been mentioned—for example, the degree of protein binding (protein-bound drug is not filtered at the glomerulus, hence is not readily excreted) and the \( V_D \) value (drugs with high \( V_D \) values are less available for renal excretion within a specific time period). Rapid drug metabolism precludes significant excretion of unchanged drug.

Drugs, like most endogenous solutes, are handled by multiple renal mechanisms, including glomerular filtration and tubular reabsorption and secretion (i.e., transport out of and into the tubule fluid, respectively). These processes are important in drug elimination. For instance, drugs that are reabsorbed often must be made more polar by metabolism before excretion can take place.

The rate of transport of a drug across the glomerular filter depends on such factors as renal plasma flow, hydrostatic pressure, and the degree of protein binding, as well as molecular size and shape and net charge. Any drug molecules that are not bound to plasma proteins can penetrate the glomerulus and enter the tubule fluid if they are small enough. Changes that decrease protein binding (such as uremia or acidosis) or the presence of other drugs may increase the amount of unbound drug available for filtration. I should add that the glomerular filtration rate declines predictably in old age, with a mean reduction of 35% between ages 20 to 25 and 75 to 80.

Many drugs are lipid-soluble. Although filtered by the glomerulus, these compounds easily cross the renal tubular epithelium by simple passive diffusion and are reabsorbed. For reabsorption by passive diffusion to occur, large concentration gradients must be created in the proximal tubule. Significant amounts of nonionized, diffusible drug can be reabsorbed (reclaimed) from the tubular fluid in this manner. Therefore, if the flow rate of di-

Drugs with Decreased Protein Binding in Renal Failure

- Aminoglycosides
- Benzonilindol
- Cisplatin
- Congo Red
- Diazepam
- Digitoxin
- Tetracyclines
- Digoxin
- Methotrexate
- Ethambutol
- Amlodipine
- Phenylbutazone
- Penicillins
- Morphine
- Sulfonamides
- Methotrexate
- Sulfonamides
- Vancomycin
- Warfarin

Drugs That May Undergo Tubular Secretion

- Antidiabetic agents
- Captopril
- Carbamazepine
- Cephalosporins
- Chlorothiazide
- Cimetidine
- Dopamine
- Ethacrynic acid
- Ethambutol
- Fluorouracil
- Tetracyclines
- Guanethidine
- Indomethacin
- Methotrexate
- Penicillins
- Phenirbamazine
- Phenytoin
- Probenecid
- Procarbazine
- Pyrazinamide
- Spironolactone
- Thalidomide
- Thiazide diuretics
- Trimethadione

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lute urine is increased, passive diffusion is diminished and renal excretion of drugs is thereby enhanced.

Drugs can also be reabsorbed by energy-dependent active transport. For instance, such agents as fluoride, bromide, and lithium salts are actively reabsorbed in the proximal tubule. Maneuvers that depress proximal reabsorption, such as osmotic diuresis and saline infusion, increase renal clearance of these compounds. On the other hand, volume depletion and sodium restriction increase tubular reabsorption and may produce toxic blood levels.

Nonionic back diffusion is another means by which drugs are reabsorbed by the renal tubules. Since many drugs are weak organic acids or bases, they may exist in either ionic or nonionic form, depending on the pKa (acidity dissociation constant) of the drug and the prevailing urine pH. For example, weak acids (of pKa<6) exist in a nonionized form in acid urine. Such drugs readily cross the cell membrane and are reabsorbed. Accordingly, raising the urine pH can be a means of retarding reabsorption and increasing tubular excretion of weak acids with low pKa, such as acetylsalicylic acid. Similarly, lowering the urine pH increases weak base excretion. The conditions that favor renal excretion of drugs through alterations in urine pH include the following: 1) pKa of the drug in the range of achievable urine pH (5 to 8); 2) normal glomerular filtration rate; 3) relatively low rate of hepatic drug metabolism.

In a number of weakly acidic or basic drugs that are excreted mainly by tubular secretion, clearance generally exceeds the glomerular filtration rate, indicating net secretion. One such drug is cimetidine, a weak organic base. Recently T. D. McKinney and associates clarified the renal handling of cimetidine in in vitro studies on proximal straight tubules of rabbits. There was active secretion of the drug from bathing fluid to tubule lumen, which was concentration-dependent. Agents that block renal organ-

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### Weak Acids and Bases That May Be Reabsorbed by Nonionic Back Diffusion

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<th>Acids</th>
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<tr>
<td>Acetazolamide</td>
<td>Amphetamines</td>
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<td>Cephaloridine</td>
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<td>Clorfrate</td>
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<tr>
<td>Saliicylic acid</td>
<td>Sulfonamides</td>
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### Metabolic Side Effects of Selected Drugs

- Acetazolamide: Magnesium load, Antacids, Absorbed antacids
- Ammonium chloride: Potassium load
- Carbenicillin: Sodium load
- Ethanol: Ampicillin/amoxicillin
- Isoniazid: Sodium polystyrene sulfate
- Methadone: Phenobarbital
- Methamphetamine mandelate: Sodium polystyrene sulfate
- Nalidixic acid: Local anesthetics, Carbenicillin, Cefalothin, Erythromycin, Phenformin
- Penicillin G: Sodium polystyrene sulfate
- Phenacetin: Acetylsalicylic acid, Carbenicillin, Cefalothin, Erythromycin, Phenformin
- Salicylic acid: Sodium polystyrene sulfate
- Sulfonamides: Calcium load
- Calcium exchange resins: Antacids
- Fluid retention: Antacids, Calcium exchange resins
- Carbamazepine: Calcium load
- Chlorpropamide: Sodium polystyrene sulfate
- Clonidine: Calcium load
- Cyproheptadine: Antacids, Calcium exchange resins
- Etoxazine: Antacids, Calcium exchange resins
- Indomethacin: Antacids, Calcium exchange resins
- Phenylbutazone: Calcium load
- Vincriot: Antacids, Calcium exchange resins
- Increases in blood urea nitrogen: Calcium load
- Androgenic steroids: Calcium load
- Glucocorticoids: Calcium load
- Estrogens: Calcium load
ic base transport (quinine and tolazoline) inhibited tubular secretion of cimetidine. In addition, inhibitors of renal organic acid transport (phlorhizin and probenecid) exerted a similar inhibitory influence on cimetidine secretion. These studies demonstrated active secretion in the straight tubules and suggested that it occurs via an organic base and, to a lesser extent, an organic acid transport system.

Clinically, use of one organic compound to retard excretion by tubular secretion of another organic compound has been in practice for years, although it may not have been recognized as such. The best example is penicillin, one of the drugs for which tubular secretion is the primary mode of excretion. In the days before long-acting penicillins became available, probenecid, which slows penicillin secretion, was useful for maintaining high plasma penicillin levels.

Although one organic acid may compete with another for secretory sites, in general there appear to be separate pathways for secretion of organic acids and bases. However, both can inhibit tubular secretion of neutral substances, such as creatinine. It should be noted, too, that drug metabolites, as well as parent drugs, may be subject to tubular secretion. In the setting of renal failure, drug excretion may be impaired if tubular secretion of a drug is damaged or if competitive drugs are present at the transport site.

Some patients with kidney or liver disease exhibit increased drug sensitivity that does not seem to be explicable on the basis of accumulation of either parent drug or active metabolites. For instance, such patients are inordinately sensitive to central nervous system depressants, such as sedative hypnotic drugs. One of the mechanisms postulated involves diminished protein binding. According to another theory, the uremic state somehow alters the blood-brain barrier.

**Fluids and Electrolytes**

Several drugs commonly used in patients with renal disease may be associated with metabolic (cation) loads, which may be administered inadvertently and in excessive amounts. Magnesium, already in excess in renal failure, is found in laxatives and antacids. Therefore, antacids without magnesium should be used. Sodium is present in many antacids, in exchange resins, and in large doses of the sodium salt of penicillin G, carbenicillin, and ampicillin. High sodium loads may produce a serious hypernatremia, especially if renal function is diminished. Potassium is found in salt substitutes and in the potassium salt of penicillin G, and high intake may cause dangerous hyperkalemia in patients with renal impairment. Hydrogen ions may be added to extracellular fluid by using ammonium chloride, ascorbic acid, para-aminosalicylate, isoniazid, and nitrofurantoin, which may lead to acid-base imbalance.

Certain drugs may cause various fluid and electrolyte disorders, particularly in patients with renal disease. To illustrate, hyponatremia can be a result of increased water intake in the presence of impaired renal excretion. This disorder may be related to faulty intrarenal mechanisms, such as decreased glomerular filtration, decreased delivery of glomerular filtrate to the ascending limb of Henle's loop (where solute-free water is generated), and decreased sodium chloride reabsorption in the same neuron segment. The other possibility is persistent antidiuretic hormone (ADH) activity in the kid-
Disposable unit-dose hydrocortisone retention enema

**Drug Information**

**Composition:** Each 60 ml unit contains hydrocortisone, 100 mg, in an aqueous solution of isotonic saline, 0.9% w/v, inactivated by sodium metabisulfite, 0.01% w/v, as a preservative.

**Indications:** Adjunctive therapy in ulcerative colitis, especially familial polyposis, proctosigmoiditis, and ulcerative colitis, proven helpful also in some cases involving rheumatoid and ascending colon.

**Contraindications:** Systemic fungal infections. Neomycin resistance.

**Warnings:** In severe ulcerative colitis, avoid delay of needed surgery pending response to medical therapy. Central insertion of enema is to be avoided to avoid rectal wall damage. Observe warnings of corticosteroid use. Increase dosage of rapid-acting corticosteroids in unusual stress; corticosteroids may mask and delay recognition of infection; prolonged use may predispose to candidiasis, gonococcal, secondary staphylococcal infections. Usage in pregnancy: Pending adequate studies, corticosteroid use in pregnant, lactating, or potentially child-bearing women requires weighing possible drug benefits against potential hazards to mother and progeny. After large corticosteroid doses during pregnancy, observe neonates for hypoadrenalism.

Hydrocortisone or cortisone therapy may increase blood pressure, sodium and water retention, effects of corticosteroids, and increase with synthetic derivatives, except in high doses. Salt restriction and potassium supplementation may be needed. All corticosteroids decrease calcium excretion. Avoid immunization procedures, especially smallpox vaccination, during corticosteroid therapy, because of possible neomycin complications and lack of antitoxin response. Observe corticosteroid-treated patient with intact tubular function or tubular dysfunction for signs of neomycin toxicity; provide hemodialysis during prolonged corticosteroid dosage.

**Precautions:** Use CORTENEMA cautiously in probability of bowel perforation, abscess or pyogenic infection, rare abscesses, obstruction, extensive fistula or sinus tracts, and in peptic ulcer, diverticulitis, renal insufficiency, hypertension, atherosclerosis and myasthenia gravis. Minimize hazard of neomycin-induced intestinal flora proliferation by reducing dosage gradually and by ascribing neomycin-related and glucocorticoid-like post-treatment stress situations. In surgical infections, consider increasing anti- microbial dosage.

Use corticosteroids cautiously in hypothyroidism, cirrhosis and ocular herpes simplex; use aspirin cautiously with corticosteroids in hyperprothrombinemia. Psychic demeansions may appear and emotional instability of psychotic tendencies may be aggravated with corticosteroid use. Carefully monitor growth of children on long-term corticosteroid therapy. Use the lowest effective corticosteroid dosage and reduce it gradually when possible.

**Adverse Reactions:** Local pain or burning, and nasal bleeding attributed to CORTENEMA have been reported rarely. Apparent exacerbations of sensitivities reactions also occur rarely. The following adverse reactions should be kept in mind when corticosteroids are given by nasal administration:

- **Fluid and Electrolyte Disturbances:** Sodium retention, fluid retention, congestive heart failure in susceptible patients; potassium losses; hypokalemia, alkalosis, hypernatremia, hypercalcemia, muscle weakness; atonic stools; loss of muscle mass; protein anions; ventricular compression fractures; acute necrosis of tendons; hematomas; intestinal tract; hypercalcemia; hypokalemia; tetany; renal tissue; and hematomas; pathologic fracture of long bones; gastrointestinal: Peptic ulcer with possible perforation and hemorrhage, paraesthesia; abdominal straining; uremic cortical calcification; perforation of the esophagus. Cholinergic: Impaired wound healing; thin fragile skin, pruritus and ecchymoses; local erythema, increased sweating; may support reactions to skin tests. Neurologic: Convulsions; increased intracranial pressure; papilledema (psuedo- tumor cerebri) usually after treatment, vertigo, headache. Endocrine: Hypoglycemic: Development of Cushinian crisis: suppression of growth in children; secondary adrenal insufficiency; and pituitary insufficiency, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. Cardiotoxic: Posterior subcapsular cataracts, intracranial pressure, glaucoma, exophthalmos. Metabolic: Negative nitrogen balance due to protein catabolism.

**Dosage and Administration:** The use of CORTENEMA Hydrocortisone Retention Enema is predicated upon the concurrent use of modern supportive measures such as rational dietary control, sedatives, antiinfective agents, antibacterial therapy, blood replacement if necessary, etc.

The usual course of therapy is one CORTENEMA nightly for 7 days, or until the patient comes to endocrinologic and psychologic improvement. Clinical symptoms usually subside promptly within 3 to 5 days. Improvement in the appearance of the mucosa, as seen by sigmoidoscopic examination and by laparoscopic examination, is the key sign of improvement. Clinical cases may require as long as 2 to 3 months of CORTENEMA treatment. Where the course of therapy extends beyond 21 days, CORTENEMA should be prescribed by a physician at the lowest effective dosage and titrated down to the minimum effective dosage, i.e., every other night for 2 or 3 weeks. If clinical or proctoscopic improvement fails to occur within 2 or 3 weeks after starting CORTENEMA, discontinue its use.

**How Supplied:** 60 ml bottles, in packages of 1 to 7, with instructions for patients.

**Note:** The administration of any corticosteroid may precipitate anaphylactic shock or other reactions, therefore care should be taken when administering any corticosteroid to patients who have a history of allergy.

**References:**

- **Aminoglycosides:** Cefazolin, Cephalaxin, Cephalothin, Carbenicillin, Methicillin, Penicillin G
- **Dicloxacillin:** Erythromycin
- **Amoxicillin:** Co-trimoxazole

**Nomogram for antibiotic therapy indicates the necessary dosage adjustment as a function of plasma clearance fraction for a particular drug and patient's creatinine clearance. For example, in patient with a creatinine clearance of 20 ml/min, adjusted maintenance dose of an aminoglycoside would be about 23% of usual dose.**

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Drug Dosage Alterations

For all the reasons mentioned—ranging from drug accumulation due to impaired biotransformation and elimination to various fluid and electrolyte disturbances—drug therapy in patients with renal disease requires utmost caution.

Obviously, one should have clear indications for using all newly prescribed drugs and, similarly, meticulous criteria for withdrawing such drugs. Medication lists must be reviewed frequently to avoid drug duplication and potential adverse drug interactions. To prevent excessive drug accumulation, the need for downward adjustment must be anticipated; drugs usually eliminated by the kidney will require the greatest reduction in dosage. Application of these general principles to a specific patient requires knowledge of the level of the patient's renal function. In this context, use of serum creatinine as the sole indicator can be misleading. When renal function is stable, serum creatinine level is determined by the rate of production and endogenous clearance. But in patients with changing renal function or those in actual renal failure, serum creatinine level may not accurately reflect renal function. For example, removal of both kidneys will result in a 1 to 2 mg/dl increase per day in serum creatinine. Although the serum creatinine will be 2 to 3 mg/dl one day after kidney removal, there is no renal function.

Other kinds of fluid and electrolyte disturbances associated with drugs are cited in the table on page 154. Awareness of the side effects and the clinical circumstances under which they arise is essential to the proper management of individuals with compromised renal function.

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Diet, corticosteroid therapy, urine flow rate, and state of catabolism are extrarenal factors that influence the BUN, making this an unsuitable parameter on which to base dosage adjustments in renal failure. In this situation, too, presuming normal renal function can result in serious overdose with drugs that have narrow therapeutic:toxic ratios.

Rather than rely on the BUN or serum creatinine level, one should look to the renal creatinine clearance as an index of kidney function and glomerular filtration rate. The requirement for a 24-hour timed urine collection to measure creatinine clearance can often be circum-
vented by estimates based on nomograms or equations. D. W. Cockcroft and M. H. Gault have devised a useful formula taking into account that creatinine excretion \(C_T\) is proportional to body mass and inversely proportional to age:

\[
C_T = \frac{(140 - \text{age}) \times \text{body weight}}{72 \times \text{serum creatinine}}
\]

where body weight is in kg and serum creatinine in mg/dl. The value calculated is reduced by 10% to 15% for women.

When possible, drug regimens should be modified by using dosage schedules previously evaluated in renal failure patients. Serum drug levels should be used to guide therapy with drugs that have narrow therapeutic index: toxic ratios, a category that includes aminoglycoside antibiotics, digitals preparations, and anticoagulants, among others. However, blood levels may poorly reflect what some drugs (e.g., antihypertensives) are actually doing—a point to keep in mind.

**Loading dose.** To ensure efficacy, the proper loading dose is usually larger than the maintenance dose of the same drug. After the first dose, the blood level will reach a steady state in an interval equal to four to five elimination half-lives. If half-life is prolonged because of impaired renal drug excretion and a loading dose is not given, there may be a delay in reaching therapeutically effective concentrations. The loading dose is especially important, needless to say, when the situation demands prompt pharmacologic action with such drugs as antibiotics, antiarrhythmics, and digitals glycosides.

There is no rule about the size of the loading dose. If such parameters as the protein binding of drug to plasma proteins and the volume of distribution are unchanged, loading dose may be the same as in patients with normal renal function. In this regard, it should be noted that the binding of digoxin to myocardial receptors is reduced in uremia, and therefore, the apparent \(V_D\) is smaller. Accordingly, most physicians recommend a cutback to one half or two thirds of the usual digitalizing dose.

**Maintenance dosage regimen.** Adjustment of drug dosage in renal disease may be necessary only when creatinine clearance goes below 30 to 40 ml/min. This is true for such drugs as cephalosporin antibiotics, which have minor side effects even with high blood levels. On the other hand, no general formula can completely prevent adverse reactions to such drugs as some cardiac glycosides and aminoglycoside antibiotics, which have low safety margins and depend entirely on renal excretion for elimination. In such circumstances, the clinician must be constantly vigilant.

There are two methods of adjusting drug regimens for patients with renal failure: 1) The usual dose is given, but the interval between doses is extended (variable-interval method), and 2) the size of the dose is reduced without changing the frequency of administration. The variable-interval method leads to more extreme peak-trough levels and is best for drugs with long half-lives. Generally, it is less complicated to lengthen the interval between doses, and most physicians select this method for all maintenance adjustments. Furthermore, although reducing the size of the dose to keep serum levels constant is appealing, the risk of adverse reactions may be increased if toxicity is related to saturable transport sites in target tissue rather than to peak serum levels.

For a drug excreted entirely by the kidney, adjustment is simple: A 50% decline in renal function necessitates either doubling the usual dosage interval or halving the dose. There are guidelines for using selected drugs that have an elimination pathway other than renal excretion. For those inclined to use them, various formulas can help in estimating the dosage of drugs for which renal excretion in unchanged form is known. For example, the formula for changing the interval between doses in renal failure is:

\[
\text{Dosage interval} = \frac{1}{f(K_f - 1) + 1}
\]

where NDI is the normal dosage interval, \(f\) is the fraction of drug normally excreted intact by the kidney, and \(K_f\) is the patient's creatinine clearance divided by normal creatinine clearance. To illustrate, if a drug is normally excreted 60% unchanged by the kidney and is given every six hours and the patient has a creatinine clearance of 10 ml/min, the adjustment would be calculated as follows:

\[
\text{Dosage interval} = 6 \times \frac{1}{0.6(0.1) + 1} = 6 \times \frac{1}{0.46} = 13 \text{ hr.}
\]

Elimination rate constants and half-life data also are published.
for commonly used drugs. With these constants, new dosage intervals for use in anuric renal failure have been calculated. In the patient who is not anephric, the elimination rate constant (k) is determined by assuming a linear relationship of the normal elimination rate constant (K) to the glomerular filtration rate. It can then be used to calculate the plasma half-life of a given drug for the degree of renal failure present, applying the formula that relates total drug clearance to half-life: K = 0.693 ÷ T.4.

The half-life data are probably most helpful in determining the frequency of administration of aminoglycoside antibiotics. Thus, for gentamicin, the steady-state serum creatinine x 7 (in mg/dl) is equivalent to two to three half-lives (in hours). For amikacin and kanamycin, the steady-state serum creatinine x 9 is approximately two to three half-lives. This approach to administering these drugs generally results in adequate, nontoxic drug levels. However, there is much variability between patients, and the aminoglycosides have a narrow therapeutic index and can induce ototoxicity. For these reasons drug level monitoring may be necessary.

Doseage nomograms have been constructed from the elimination rate data and applied to all levels of renal function. They are based on the three types of elimination of drugs—exclusive renal clearance, predominant nonrenal clearance, and a combination of renal and nonrenal. The nomograms on pages 155 and 157 exemplify all three types.

Whether one uses the various formulas, half-life data, or nomograms, it must be kept in mind that they are only guides and not substitutes for observation of clinical response and toxicity in individual patients. Moreover, all of the mathematical constructs are contingent on several assumptions: 1) that the rate of elimination per unit of time is proportional to the amount of drug in the body; 2) that the uremic state does not influence extrarenal drug removal; 3) that clinical measurement of the glomerular filtration rate accurately reflects reduced renal elimination of the drug; and 4) that the metabolic products of drug biotransformation lack pharmacologic activity of their own.

These assumptions are simplistic and are likely to be invalid especially in the uremic state. There is a need for close clinical, biochemical, and drug level monitoring of patients with renal failure, regardless of the method used to modify the drug dosage regimen.

Drugs and Dialysis

Drug prescribing is complicated when patients with renal failure are on dialysis, since they may lose therapeutic levels of some drugs in the dialysis bath. (It is noteworthy that dialysis can serve as a means of treating patients with drug intoxication.) Many factors contribute to the rate of drug removal, such as dialyzer type, surface area, membrane characteristics, dialysate flow rates, and specific properties of the drug in question (such as molecular size and net charge). Drug availability—which depends on the V_d and the percentage of protein binding—and the rapidity of intercompartmental transfer also enter into the evaluation. All of these factors influence the amount of drug removed during dialysis. In certain instances, for other reasons such as duration of action, there is no need to replace the loss, even when a drug is dialyzable.

Several methodologic problems have made it difficult to obtain an accurate data base with respect to drugs and dialysis. Substantial differences between the total amount of drug in the dialysate and the total removed, as calculated by dialyzer clearance or dialysance values, have been observed. Clearance techniques usually underestimate dialyzer drug removal, as quantified by recovery techniques. It is possible that dialysis may result in the removal of drugs from blood cells as well as from plasma, and this could perhaps account for some of the discrepancies. From a practical standpoint, information on drug removal during dialytic therapy is still being collected and at present can be related to clinical situations only in a general way.

For drugs that may be substantially removed by dialysis, a sensible rule to follow is to administer maintenance doses at the conclusion of a dialysis treatment. If a drug is dialyzable and sustained serum levels are necessary, projected dialysis losses must be replaced.

At all levels of renal failure, determination of the glomerular filtration rate by endogenous creatinine clearance provides the best basis for modifying drug dosage. Maintenance adjustments, which are usually made by lengthening the interval between doses, usually cannot be expressed by a fixed formula but must be tempered by sound clinical judgment and a knowledge of the pharmacologic and potential toxic effects of the drugs being used. With this approach, drug therapy can be used with greater safety and efficacy.

Selected Reading