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DRUG THERAPY IN RENAL FAILURE

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INTRODUCTION

Patients with poor renal function can develop any other acute or chronic illness in addition to their kidney abnormality. Treating these patients with the usual drugs or dosage designed for people with normal kidney function often results in toxicity or lack of efficacy.

There are a number of reviews available detailing the use of specific drugs in renal failure (1–6). These classify the drugs by their therapeutic use and enable an individual to look up a specific drug to learn how its usual dose must be modified for a patient with renal failure. The purpose of this review is to present this information about drugs using a classification based on the major pathway of elimination or other dispositional characteristic of the drug. By doing this, certain generalizations emerge that can be used to predict the behavior of a drug in a patient with renal failure.

EXCRETION OF UNMETABOLIZED DRUG

A number of drugs are eliminated from the body mainly by urinary excretion of the unmetabolized, pharmacologically active drug. Some of these are listed in Table 1. All drugs with urinary excretion as their major pathway of elimination will accumulate in patients with renal failure. This accumulation during a course of treatment will lead to an increased intensity of effect over what would be expected in a patient with normal kidney function. For this reason, dosage of an excreted drug should be reduced in proportion to the decrease in renal function of the patient.

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Table 1 Some drugs with renal excretion as a major pathway of elimination (6, 7)

Ampicillin	Kanamycin
Carbenicillin	Methotrexate
Cephalexin	Methyldopa
Cephalothin	Neomycin
Cephazolin	Procainamide
Colistin	Streptomycin
Cycloserine	Sulfinpyrazone
Digoxin	Tetracycline
Ethambutol	Tobramycin
5-Fluorocytosine	Vancomycin
Gentamicin	

BIOTRANSFORMATION OF DRUGS IN RENAL FAILURE

The plasma half-life values of many drugs have been measured in patients with renal failure and compared to values from normal subjects. A compilation of these studies with the drugs classified by their major pathway of metabolism is presented in Table 2. The major drug metabolism pathway of oxidation followed by glucuronide or sulfate conjugation, in general, is normal in renal failure.

Phenytoin, however, has markedly accelerated metabolism in uremia. Patients with renal failure require larger than average doses of this drug to achieve the usual intensity of effect. Some of the studies of antipyrine and propranolol also indicate rapid oxidative metabolism in uremic patients. Other studies such as the one with pentobarbital indicate that some uremic patients have rapid oxidation while most patients' values fall within the normal range. The reasons for this accelerated oxidative drug metabolism in uremic man have not yet been discovered. This acceleration of oxidation in man stands in sharp contrast to the slowed oxidative drug metabolism observed in experimental renal failure in laboratory animals (8, 46, 47).

Quinidine, which is eliminated by oxidation, appears to be an exception to the generalization of normal or rapid oxidation in uremia. While its half-life is normal in patients with renal failure (23), its total body clearance, a better measure of metabolism, is reduced (24).

The data in Table 2 indicate that drugs that follow the same pathway of elimination will, in general, have their elimination rates affected in a similar way in uremia. Oxidations, for the most part, appear to be normal or accelerated. Reduction is slowed. Conjugation with glucuronic acid, sulfate, or glycine, appear normal while acetylations are often slow. The hy-

Table 2 Effects of renal failure on elimination of metabolized drugs

Drug	Effect	Reference
	Oxidations	
Antipyrine	Normal or rapid	8, 9
Digitoxin	Normal or rapid	10
Histamine	Normal	11
Lidocaine	Normal	12, 13
Meperidine	Normal	14
Pentobarbital	Normal	15
Phenacetin	Normal	19
Phenobarbital	Normal	16
Phenytoin	Rapid	17, 18
Propranolol	Normal or rapid	20–22
Quinidine	Normal or slow	23, 24
Tolbutamide	Normal	25, 26
Xylitol	Normal	27
	Reduction	
Cortisol	Slow	28
	Synthesis	
	(Glucuronide Conjugation)	
Acetaminophen	Normal	30
Chloramphenicol	Normal	29
Lorazepam	Normal	31
	(Sulfate Conjugation)	
Acetaminophen	Normal	30
Methyldopa	Normal	32
	(Acetylation)	
p-Aminosalicylate	Slow	33
Isoniazid	Normal or slow	34–36
Sulfisoxazole	Slow	37
	(Glycine Conjugation)	
Salicylate	Normal	38
	Hydrolyses	
	(Peptides)	
Glucagon	Slow	42
Insulin	Slow	39–41
	(Esters)	
Cephalothin	Slow	44
Clindamycin phosphate	Slow	45
Procaine	Slow	43

drolyses seem slowed. Thus, if one knows the major pathway of elimination of a drug in man, one can predict the probable effect of uremia on its rate of elimination.

ACTIVE DRUG METABOLITES

Pathways of drug metabolism have been considered "detoxication mechanisms" in the past. The implication has been that the products of these biotransformation reactions have had no pharmacologic activity. While this is true for a great many drug metabolites, others do have pharmacologic activity. Drayer (48) has compiled a list of drugs that have active metabolites. When urinary excretion is the major pathway of elimination of the active metabolite, it will accumulate in patients with renal failure given the parent drug. If the metabolite has the same pattern of pharmacologic response as the parent, the patient will appear to have an enhanced intensity of effect. If the metabolite has a pattern of pharmacologic activity different from that of the parent drug, the effects observed may differ qualitatively as well as quantitatively from what was expected. A few examples of this have been demonstrated in man.

The N-acetylated metabolite of procainamide has antiarrhythmic activity similar to procainamide (49, 50). It is eliminated from the body almost entirely by urinary excretion (51). Thus, one would expect it to accumulate in patients with renal failure given procainamide and cause an apparently greater intensity of effect than one would expect for the procainamide dose or procainamide concentration in serum of the patient. Observations in dialysis patients receiving procainamide confirmed these expectations (52).

Oxypurinol contributes significantly to the pharmacologic effect of allopurinol in man. Thus, patients with renal failure have increased oxypurinol which contributes to their xanthine oxidase inhibition. Patients with renal insufficiency who take full doses of allopurinol appear to have a high incidence of side effects which may be due to the accumulation of oxypurinol (53).

Chlorophenoxyisobutyric acid, the free acid metabolite of clofibrate, appears to be the active principle of clofibrate therapy. It accumulates substantially and causes a myopathy when clofibrate is given in usual doses to patients with renal failure (54). A mechanism in addition to simple failure to excrete this acid has recently been identified as a major cause of high levels of this compound in renal failure patients given clofibrate. Normally, the clofibrate free acid is conjugated with glucuronic acid and both compounds are excreted in the urine. Gugler observed that the serum of uremic patients given clofibrate contained high levels of the glucuronide conjugate and that plasma from uremic patients hydrolyzed this glucuronide back to

the free acid (55). This, then, is an example of failure to excrete a metabolite of a drug (the conjugate) with subsequent biotransformation (hydrolysis) of the metabolite back to the active compound leading to its accumulation in renal failure.

Normeperidine is a metabolite of meperidine that is less analgesic but more convulsant than its parent, meperidine. It is eliminated by urinary excretion or ester hydrolysis, both pathways being slowed in uremia. Normeperidine accumulates in patients with renal failure given multiple doses of meperidine. In some of these patients, tremors or seizures, apparently due to the high levels of normeperidine, occurred (56). Recent studies of normeperidine levels in cancer patients receiving meperidine chronically have revealed that some patients with tremors or seizures have high levels of this metabolite (57). Thus studies of accumulation of this active metabolite in renal failure have led to studies of its accumulation and action in patients with other diseases.

The metabolite 2-hydroxychlorpropamide is active and normally excreted in the urine (58). Its slowed excretion in renal failure probably is the reason for the long duration of chlorpropamide effect in patients with poor renal function.

Uremic patients given digitoxin have low serum levels of this drug but accumulate digoxin (an active metabolite of digitoxin) to the extent that therapeutic serum levels of it were present (59).

Hydroxyamobarbital has been observed to accumulate in serum of uremic patients given amobarbital. This metabolite has about one third the hypnotic potency of amobarbital and has been incriminated as the cause of impaired cognitive function in uremic patients given the parent drug (60).

PROTEIN BINDING OF DRUGS IN UREMIA

Changes in the binding of drugs to plasma proteins can cause changes in various pharmacokinetic parameters of drugs (61–63). A decrease in the binding of a drug can cause an increase in the volume of distribution of the drug when the volume of distribution is calculated as the ratio of the amount of drug in the body to the drug concentration in the plasma. For drugs with high hepatic extraction ratios, decreased plasma protein binding can cause a decrease in hepatic drug clearance. Conversely, drugs with low hepatic extraction ratios, such as phenytoin, can have their hepatic clearance increased when their protein binding decreases (63).

Plasma from patients with renal failure have decreased protein binding of acidic drugs (Table 3). This decrease in protein binding is greater than can be accounted for by any decrease in serum protein concentration. Therefore, it must be due to either displacement of the drug from protein

Table 3 Acidic drugs that have decreased binding to plasma proteins from patients with renal failure (15, 64–67)[a]

Benzylpenicillin	Phenol red
Clofibrate	Phenylbutazone
Congo red	Phenytoin
Diazoxide	Salicylate
Dicloxacillin	Sulfonamides
Fluorescein	Thiopental
Methyl orange	Thyroxine
Methyl red	Tryptophane
Pentobarbital	Valproic acid
Phenobarbital	Warfarin

[a] Indomethacin has normal binding.

binding sites by other compounds (68–71) or by change in the nature of the binding proteins themselves (72, 73). Renal transplantation leads to rapid improvement in the binding of acidic drugs to plasma proteins (67, 74, 75).

The concentration of a drug in plasma water is what establishes the diffusion gradient to its site of action and hence its intensity of effect. A decrease in protein binding will cause an increase in this "effective" concentration for any measured concentration of drug in plasma since all the methods for measuring plasma levels of drugs measure drug bound to plasma proteins as well as drug in plasma water. Thus, when measurements of the concentrations of acidic drugs in plasma are used to individualize therapy for patients with renal failure, allowance for this decreased binding must be made in the interpretation of the measured values.

Renal failure has a variable effect on the protein binding of basic drugs (Table 4). Interpretation of serum levels of these drugs in uremic patients requires knowledge of the specific drug.

Table 4 Binding of basic drugs to plasma proteins from patients with renal failure (64, 65)

Drug	Binding
Dapsone	Normal
Desmethylimipramine	Normal
Diazepam	Decreased
Morphine	Slight Decrease
Propranolol	Normal
Quinidine	Normal
Triamterene	Decreased
Trimethoprim	Normal
d-Tubocurarine	Normal

CONCLUSIONS

If one evaluates the information about drug therapy in renal failure using a classification of drugs based on their dispositional characteristics, a series of generalizations emerges. Drugs that are excreted unchanged by the kidneys and active drug metabolites that are normally eliminated by urinary excretion will accumulate in renal failure. Allowance must be made for this in establishing dosage regimens for drugs in these classes. Drugs eliminated by oxidation will usually be eliminated at the normal rate. Some uremic patients have accelerated drug oxidations and some drugs, particularly phenytoin, have very rapid oxidation in nearly all uremic patients. The other pathways of drug metabolism seem normal or slowed in uremia. The binding of acidic drugs to plasma proteins is decreased in renal failure while that of basic drugs is variable. Knowledge of this binding is necessary for the clinical interpretation of measurements of serum levels of drugs in patients with renal failure.

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