Chapter

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Drug Dose Adjustment in Chronic Renal Diseases

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INTRODUCTION

The development of numerous drugs over the last two decades to a variety of diseases with significant benefits has paralleled increasing awareness of the adverse effects of these drugs. Majority of the drugs are eliminated by the kidneys. Therefore it is mandatory to make appropriate dosage modification when renal function deteriorates to prevent drug toxicity. Dosage modification tables of large number of drugs that are affected by chronic kidney disease (CKD) are available in medical literature and they are also provided by the pharmaceutical industry.

The action of a drug is related to its free form concentration in the tissues. The bio-availability of the drug depends on the route of administration, absorption factors in the gut and bio-transformation in the liver.

WHY DRUG DOSE ADJUSTMENT IN CHRONIC RENAL DISEASE?

The uremic millennium alters the drug absorption and bio-availability, drug distribution and clearance. Gastrointestinal drug absorption can be impaired due to vomiting, diarrhea, decreased gastric acidity, delayed gastric emptying and following the use of phosphate binders that bind or chelate drugs. Expanded extracellular volume status that is common in chronic renal failure such as edema and ascites can increase the volume of distribution of therapeutic agents. Other factors that affect drug distribution are molecular size, plasma protein binding and drug tissue binding.

Total plasma drug concentration may under estimate free drug levels and therapeutic response because of decreased binding to albumin. For example, phenytoin sodium that is poorly bound to albumin in chronic renal failure (CRF) may be estimated to be below therapeutic levels in total plasma and increase in the dose of phenytoin sodium based on this report would lead to toxicity (Fig. 1). But in chronic kidney disease organic acids, normally excreted in the urine, accumulate and compete with phenytoin for binding sites on albumin molecules. Uremia also changes the shape of albumin molecules (and that of other serum proteins), affecting phenytoin attachment. Moreover, patients with chronic kidney disease may have hypoalbuminemia. All of these

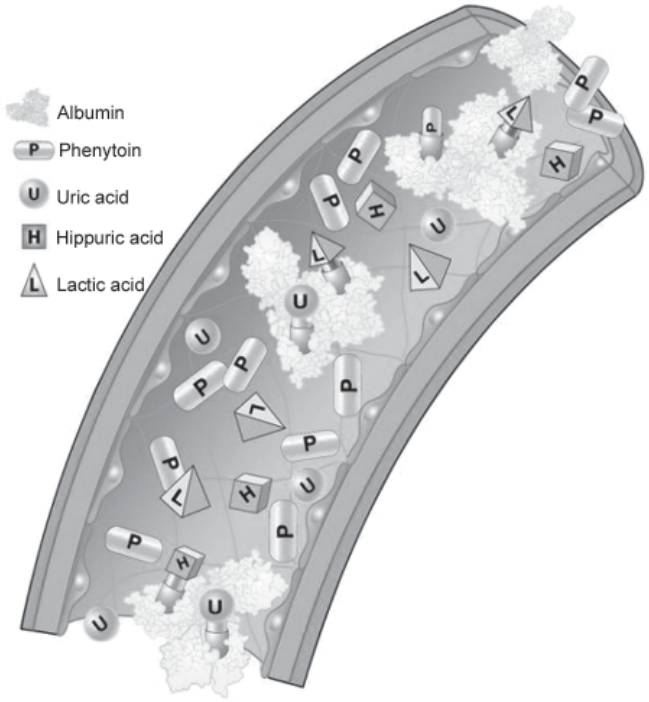

Fig. 1: Altered protein binding of phenytoin in CKD

changes result in significantly limited binding of phenytoin to albumin and greater distribution of the drug to other tissues.

Specific measurement of free phenytoin concentration would help optimize therapeutic dosage and avoid toxicity.

In addition to performing excretory and endocrine functions, the kidneys also produce numerous enzymes involved in drug metabolism, including the cytochrome P-450 (CYP) enzymes. Although the liver is the main producer of these enzymes, the kidneys may contribute up to 18% of total CYP-activated drug metabolism. In addition, the kidneys have been shown to be involved in the glucuronide, glutathione, and sulfate conjugation reactions that occur during drug metabolism.

Often metabolites of the drug are pharmacologically active or cause toxicity, and renal insufficiency may result in their unanticipated accumulation. Meperidine, for example, is extensively metabolized, and renal failure has little effect on its plasma concentration; however, its metabolite, normeperidine, accumulates above its usual level when renal function is impaired. Because normeperidine has greater convulsant activity than meperidine, this accumulation probably accounts for the signs of central nervous system (CNS) excitation, such as irritability, twitching, and seizures, that appear when multiple doses of meperidine are administered to patients with renal disease.

Some hepatically metabolized drugs have active metabolites that are excreted renally. In renal impairment these metabolites can accumulate and lead to drug toxicity. For example, the pain reliever acetaminophen (Tylenol and others) yields the metabolite N-acetyl-p-benzoquinoneimine; accumulation results in hepatotoxicity. The antiarrhythmic procainamide (Procan SR and others) yields N-acetylprocainamide; accumulation can cause cardiac toxicity.

THE PRINCIPLES AND PRACTICE OF DRUG MODIFICATION IN CHRONIC KIDNEY DISEASES

Total plasma clearance of the drug depends on renal elimination and metabolic transformation in the liver. Renal elimination of drugs is determined by glomerular filteration rate (GFR), tubular reabsorption and secretion. Drugs with primary hepatic elimination are generally preferred although renal insufficiency may affect hepatic drug metabolism.

It is hard to predict accurately the pharmaco-kinetic parameters of a drug in a recipient. However, a reasonable estimate of the plasma clearance of a drug in CRF can be made if the renal and plasma clearances of the drug in patients with normal renal function are known.

It is neither practical nor possible to measure GFR (Glomerular Filtration Rate) everywhere by sophisticated investigations to assess renal function. We can use serum creatinine or creatinine clearance for indirect estimation of GFR. For this purpose various formulae are available. Here we are giving two very simple formulae to calculate GFR.

1. Creatinine clearance = $\frac{0.48 \times \text{height (cm)}}{\text{Serum creatinine (mg/dl)}}$

(Normal creatinine clearance = 130 ml/minute/1.73 m^2)

One of the problems with using serum creatinine or its inverse value as a measure of glomerular filtration rate is that interpatient and intrapatient differences in creatinine production often occur. Variations in creatinine production due to age and sex, related differences in muscle mass have been incorporated in formulae to improve the ability of serum creatinine to estimate GFR.

2. Cockcroft and Gault's formula

A drug renal clearance is proportional to creatinine's clearance (Clcr), which may be measured directly or estimated from the serum creatinine level (Ccr). In men:

$$\text{Clcr} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{Ccr (mg/dl)}} \text{ (mL/min)}$$

For women, the estimate by the above equation should be multiplied by 0.85 to reflect their smaller muscle mass. It should also be noted that this equation is not valid for patients with severe renal insufficiency (Ccr < 5 mg/dl) or when renal function is changing rapidly. For simplicity, normal creatinine clearance is conveniently considered to be 100 ml/min. Thus, if the relative contributions of renal and nonrenal elimination to systemic clearance are known, an appropriate modification of the dose in a patient with a given level of insufficiency can be estimated. For example, if the fraction of drug excreted unchanged is 0.9 and creatinine clearance is reduced to 10% of normal, the dosing rate should be reduced to 19% of normal. This modification, which in practice would be rounded to 20%, is based on the fact that nonrenal clearance is unchanged (10% of normal clearance); renal clearance is reduced from 90% to 9% of normal Cl; thus systemic clearance is reduced to 10+9 =19% of normal Cl.

In clinical practice today, most decisions involving dosing adjustment in patients with renal failure use published tables of recommended dosage reduction of

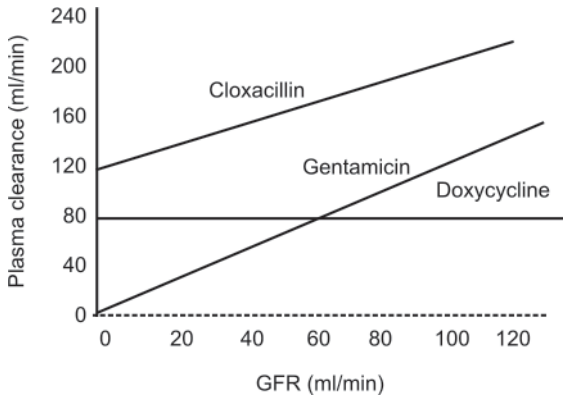

Fig. 2: The relationship between plasma clearance and GFR for a few drugs. Elimination of doxycycline is independent of renal function, and cloxacillin has a large extrarenal clearance (from Cutier and Forland)

dosing interval lengthening based on the level of renal function indicated by Clcr, or similar information provided in the drug "label". Such modifications are, however, rigorously based on pharmacokinetic principles and are best used when resulting plasma concentration data and clinical observation are used as necessary, to further optimize therapy for the individual patient.

Plasma clearance could be in three forms, (i) mainly renal, (ii) mainly non-renal and (iii) combination of renal and non-renal. Gentamicin is eliminated almost entirely by the renal route. Doxycycline is excreted mainly by the non-renal route whereas Cloxacillin is eliminated both by the renal and non-renal routes (Fig. 2).

The dosage regime is aimed to achieve one of two objectives, (i) to reach the same maximum and minimum blood levels or (ii) to achieve similar amount of drug in the body during a given dosage interval for both normal and renal failure patients. The following strategies may be used to obtain the above objectives.

i. Increase of dosage intervals without changing the dose
ii. Reduction of the dose without changing the frequency and
iii. Combination of both Increase of dosage intervals and dosage modification

DRUG DOSAGE MODIFICATION IN PATIENTS WITH RENAL INSUFFICIENCY

i. The loading dose is the same for patients with normal renal function and those with chronic renal insufficiency as it depends only on the volume of distribution(Vd) and not on the drug clearance except in those with expanded extracellular fluid volume who would require a larger loading dose.
ii. The maintenance dose is the fraction of the normal dose in renal insufficiency and can be calculated as follows:
    a. Dose in renal failure = Dose in normal renal function x (t½ normal/t renal failure)

       Where t½ is the half-life for elimination and inversely proportion to clearance.

       Or
    b. The Dose is constant and the dosing interval increased

       Dose interval in renal failure = normal dose interval/(t½ normal/ t½ renal failure)

Now after calculating creatinine clearance and having a approximate idea of GFR, we will discuss common drugs used in disorders of different systems of body. In clinical practice dosage adjustments in renal failure can be made based on GFR estimation with Cockroft-Gault formula and from the dosage and frequency of drug administration obtained from the below illustrated Table 1.

Care must be exercised in elderly patients who have often compromised renal function that is not clinically evident. Drugs such as nalidixic acid and nitrofurantoin are contraindicated in patients with renal failure as they have narrow therapeutic versus toxic margin. Aminoglycosides and nonsteroidals are to be used with caution as aminoglycosides are potentially nephrotoxic and required dosage modification. Long-term use of nonsteroidals may be associated with analgesic nephropathy. The use of ACE inhibitors is restricted in advanced renal failure as they reduce GFR and may worsen hyperkalemia.

CARDIOVASCULAR DRUGS

Digoxin

The most important determinant of the daily digoxin dosage in all age groups is renal function. In severe renal insufficiency, there is a decrease in the volume of distribution of digoxin so that it is not exact to use a nomogram to estimate the maintenance dose based on creatinine clearance. One practical policy is to start with a maintenance dose of 0.125 mg/day in patients with severe renal insufficiency and rely on serum digoxin levels, for dose adjustment.

Table 1: Dose or frequency adjustment based on calculated GFR (ml/min)

Drug	*(%) Excreted Unchanged*	*(%) Protein bound*	*t1/2 Normal/ renal failure (h)*	*GFR (ml/min) >50*	*10-50*	*<10*
Analgesics/ Non-steroidals/ Narcotics						
Aspirin	Hepatic/renal	80-90	2-3/unchanged	q4h	q4-6h	Avoid
Paracetamol	Hepatic	20-30	2/2	q4h	q6h	q8h
Rofecoxib	Hepatic	85	17/unchanged	qd	avoid	avoid
Codeine	Hepatic	7	2.5-3.5/?	100%	75%	50%
Morphine	Hepatic	20-30	1-4/unchanged	100%	75%	50%
Aminoglycosides						
Amikacin	95	<5	1.4-2.3/17-150	60-90%	30-70%	20-30%
Gentamicin	95	<5	1.8/20-60	60-90%	30-70%	20-30%
Cephalosporin						
Cefatoxime	60	37	1.0/15	q6h	q8-12h	q24h
Ceftazidime	60-85	17	1.2/13-25	q8-12h	q24-48h	q24h
Quinolones						
Ciprofloxacin	50-70	20-40	3-6/6-9	100%	50-75%	50%
Antifungal						
AmphotericinB	-	90	24/unchanged	q24h	q24h	q24h-36h
ACE-inhibitors						
Captopril	30-40	25-30	1.2/21-32	100%	75%	50%
Ramipril	10-21	55-70	5.8/15.0	100%	50-75%	25-50%
Anti-diabetic						
Chlorpropamide	47	91-99	24-48/50-200	50%	avoid	avoid
Metformin	90-100	Negligible	1-5/prolonged	50%	25%	avoid

Patients with acute renal failure should be considered to have GFR less than 10% and dosage modifications of drugs can be made on this estimate.

Creatinine clearance	*Approximate dose*
10-12 ml/mt	0.125 mg/day
26-49 ml/mt	0.1875 mg/day
50-79 ml/mt	0.25 mg/day

As example, for a 70 kg male aged 70, the "estimated" digoxin dose is 0.25 mg for serum creatinine upto 1.5 mg/dl and 0.125 mg when the creatinine exceeds about 3.0 mg/dl. These values are only approximations, stressing the important role of renal function in determining digoxin dosage.

LIDOCAINE

Therapeutic plasma concentration is 1.5-5.0 µg. It has 90% hepatic excretion. Half life in renal failure slightly raised. Adjustment in renal failure not needed. Removal by dialysis not possible due to high protein binding.

AMIODARONE

Therapeutic plasma concentraton is 0.5-3.0 µg, 100% hepatic excretion. Half life is 53 days. More than 95% protein binding, can be used during renal failure. For procainamide, disopyramide, tocainide, mexiletine adjustment for renal failure needed (plasma concentration measurement done).

BETA-BLOCKERS

For atenolol, nadolol, sotalol dose adjustment for renal failure is needed. May accumulate in renal failure. Removal by hemodialysis is possible. For acebutolol,

alprenolol, metoprolol, oxprenolol, pindolol, propranolol, timolol, esmolol dose adjustment for renal failure is not needed. They all have hepatic excretion.

CALCIUM CHANNEL BLOCKERS

For verapamil, diltiazem, nifedipine, nicardipine and nimodipine dose adjustment for renal failure is not needed. They all have hepatic excretion.

METHYLDOPA

There is retention of active metabolities in renal failure because excretion is by renal route. Dose adjustment is needed when creatinine clearance < 50 ml/mt. Removal by dialysis possible.

CLONIDINE

Excretion is mainly by renal route, dose adjustment is needed when creatinine clearance < 10 ml/mt. Removal by dialysis not possible. Rebound hypertension can occur if drug stopped abruptly. For prazosin, nitroglycerin s/l and nitroprusside dose adjustment for renal failure is not needed. They have hepatic excretion.

Thiazides	May be ineffective when creatinine clearance < 30 ml/mt. Dose adjustment in renal failure needed.
Furosemide Ethacrynic Acid	Both of them needed in large doses in renal failure. Can be removed by dialysis.
Triamterene Spironolactone	Dose adjustment in renal failure is needed. Avoid when creatinine Clearance < 30 ml/mt. May cause hyper kalemia.
Anticoagulants	
Heparin Warfarin	Dose adjustment in renal failure is not needed. They may potentiate Uremic bleeding.
Enoxaparin	Empirical dose adjustment of Enoxaparin may reduce the risk for bleeding.
Streptokinase	Dose adjustment is not needed. May potentiate uremic bleeding
Cholestyramine Cholestipol	Dose adjustment not needed but may cause hyperchloremic acidosis
Gemfibrozil Nicotinic Acid	Dose adjustment is needed
Lovastatin	Lovastatin can be given if needed. Route of excretion is mainly Hepatic.

PROKINETIC AND ANTIEMETIC AGENTS

Metoclopramide

The half life is about 4 to 6 hours, but it may be as much as 24 hours in patients with impaired renal function so dose spacing is necessary.

Domperidone

Domperidone appears to be rapidly absorbed after oral administration but its bioavailability is only about 15%. Most of the drug and its metabolites are excreted in the feces, more safe in renal failure.

ANTIPSYCHOTICS, ANTIDEPRESSANTS, BENZODIAZEPINES

All of them mainly have hepatic or enterohepatic excretion but their sedative properties demand caution in renal failure. Chlorpromazine has a unique action in suppression of hiccough. Most of them have high protein binding so even removal by dialysis is not possible.

METHYL XANTHINES AND AMINOPHYLLINES

Methyl Xanthines are eliminated primarily by metabolism in the liver. Less then 20 and 5% of administered theophylline and caffeine respective are recovered in the urine unchanged. Methyl xanthines especially theophylline, increase the production of urine and the patterns of enhanced excretion of water and electrolytes are very similar to those produced by the thiazides. In most animal studies theophylline has been found to increase the GFR and renal blood flow. However, the influsion of aminophylline (3.5 mg/kg) into normal human subjects appears to inhibit solute reabsorption in both the proximal nephron and the diluting segment without changing appreciably either GFR or total renal blood flow. No additional effects are produced by theophylline in the presence of furosemide. By contrast, the administration of aminophylline does produce additional excretion of Na^+, Cl^- and K^+ in patients with CHF during treatment with diuretics, so they can be used in renal failure if needed.

ASPIRIN-LIKE DRUGS

Aspirin-like drugs have little effect on renal function in normal human subjects presumably because the production of vasodilatory prostaglandins because the production of vasodilatory prostaglandins has only a minor role in Na^+ replete individuals. However these

drugs decrease renal blood flow and the rate of glomerular filtration in patients with CHF, hepatic cirrhosis with ascites, or CRF or in those who are hypovolemic for any reason. ARF may be precipitated under these circumstances. In all of these settings renal perfusion is more dependent upon prostaglandins that cause vasodilation and that can oppose the vasoconstrictive influence of norepinephrine and angiotensin II that result from the activation of pressure reflexes.

In addition to their hemodynamic effects in the kidney aspirin like drugs promote the retention of salt and water by reducing the prostaglandins induced inhibition of both the reabsorption of chloride and the action of antidiuretic hormone. This may cause edema in some patients who are treated with an aspirin like drug. It may also reduce the effectiveness of antihypertensive therapy. These drugs promote hyperkalemia by several mechanisms including enhanced reabsorption of K^+ as a result of decreased availability of Na^+ at distal tubular sites and suppression of the prostaglandins induced secretion of rennin. So these are best avoided, if necessary can be given in low doses, and on SOS basis.

As acid peptic disease is found in ¼ of renal failure patients, it is very important to note that all the NSAIDs except P-aminophenol derivative, have a tendency to cause gastrointestinal side effects which may range from mild dyspepsia and heart burn to ulceration of the stomach or duodenum, sometimes with fatal results. Para aminophenol derivatives when used in optimal doses are safe and effective antipyretic – analgesics. They do not cause APD, but in overdoses they can cause ATN.

INSULIN, ORAL HYPOGLYCEMIC AGENTS

In true insulin dependent diabetics, there is often a decrease in insulin requirement with progressive azotemia, a phenomenon not related solely to decreased caloric in take. The hypoglycemia of renal failure has multiple causes, in addition to impairing substrate delivery, uremic toxins may suppress hepatic gluconeogenesis and decreased renal clearance of insulin.

Chronic kidney disease significantly alters insulin metabolism. In people with diabetes without kidney impairment, the kidneys metabolize about 30% of an insulin dose. But in patients who have both diabetes and kidney disease, insulin metabolism decreases with diminishing kidney function: in stages 3 or 4 chronic kidney disease, an insulin dosage reduction of 25% may be indicated, and in those in stage 5 it may need to be reduced by 50% or more. Of course, insulin dosage adjustments should be based on patient response and blood glucose monitoring.

Sulfonylureas

In patients who have significant renal disease, it is preferable to treat with tolbutamide and tolazamide, since these agents are exclusively metabolized and inactivated by liver.

Biguanides

Biguanides should not be given to patients with renal disease and should be stopped if nausea, vomiting, diarrhea or any intercurrent illness appears.

ANTITUBERCULAR DRUGS

Patient with CRF also present special treatment problems and these patients have tuberculosis case rates approximately 10 times those of general population. In patients with renal failure isoniazid should be reduced to 5 mg/kg body weight two or three times weekly. Patient on dialysis should receive the drug following each dialysis. In severe renal failure INH should be given with pyridoxine. Ethambutol behaves like isoniazid except that it is excreted as active drug. As with isoniazid, the usual daily dose should be given at longer intervals and administration should follow dialysis. Patient with renal failure who are receiving ethambutol should have their color vision and visual acuity monitored regularly. Rifampin is protein bound, non dialyzable, excreted in the bile by the liver. No change in dose or interval is necessary. Pyrazinemide also can be given once daily if GFR > 10 ml/mt and every 2-3 days if GFR < 10 ml/mt. In case of streptomycin (known nephrotoxic substance, better to avoid) it can be given once daily if GFR > 50 ml/mt, in every 3-4 days if GFR less then 10 ml/mt. Ciprofloxacin can be used in renal failure in full doses upto GFR > 50 ml/mt, 50% dose upto GFR > 10 ml/mt and in 30% dose if GFR is < 10 ml/mt. As per WHO recommendations the regimen is 2RHZ/6HR.

DIAGNOSTIC PROCEDURES (CONTRAST MEDIA)

Although the use of nephrotoxic agents in this population is discouraged, it's sometimes unavoidable. For example, some diagnostic procedures (such as IV pyelogram and some computed tomographic scans)

require the use of contrast dye, which is nephrotoxic in everyone. In people with chronic kidney disease, it can hasten the onset of stage 5 and the need for dialysis. Several measures have been aimed at reducing the nephrotoxic effects of contrast media—IV saline hydration, N-acetylcysteine, the iso-osmolar contrast agent iodixanol, and hemofiltration—with varying results (some were quite costly). And in a recent randomized study, IV hydration using sodium bicarbonate was more effective than sodium chloride for preventing contrast nephropathy.

Prescribing for Patients on Hemodialysis

Drug removal is directly proportional to the plasma concentration of free drug and membrane characteristics of the dialyzer. The most important variables limiting drug removal are large Vd and high protein binding in hemodialysis.

Drug Therapy During Continuous Renal Replacement Therapy (CRRT)

Patients on CRRT may be considered to have a creatinine clearance in the range of 30 to 35 ml/min and dosage adjustments can be made from a reference table. The 24 hr creatinine clearance is obtained from the total dialysate or ultra filtration volume.

Prescription of Drugs to Patients on Peritoneal Dialysis

The rate on peritoneal drug clearance of many drugs are inconsistent increasing the need for drug level monitoring. Drug removal is slow and poor with continuous ambulatory peritoneal dialysis (CAPD).

CONCLUSION

In conclusion the habit of routine estimation of GFR and reference to the tables of drugs that are affected by CKD along with confirmation of the estimates with plasma drug levels would be good clinical practice in prescribing drugs in patients with chronic renal failure.

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