Drugs in renal failure

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When prescribing a drug for a patient with renal failure, many issues must be considered before giving any advice or recommending any dosage changes in such a condition. This is one of the problems tackled by medicine information pharmacists. A drug may behave differently in a patient with renal dysfunction from a patient with normal function. This article helps to highlight some of the basic principles that we need to keep in mind when dealing with information about drugs in renal disease.

Renal failure is a condition in which many factors are involved in altering a drug's pharmacokinetics, inducing changes in the absorption of the drug, plasma protein binding, volume of distribution, excretion, drug sensitivity and tissue distribution. Thus when prescribing a drug in such a condition, one must keep some basic principles in mind.

Acute renal failure may be defined as the cessation of renal excretory function within a period of hours or days, accompanied by a rise in serum urea and creatinine. It may be accompanied by a fall in urine output, presenting itself as anuria or oliguria. The causes of acute renal failure may be classified as pre-renal, renal and post-renal damage.

Pre-renal damage occurs when the kidneys are deprived of blood flow. Drugs can cause this type of damage by compromising the circulation and hence decreasing renal perfusion. Volume depletion resulting from aggressive diuretic therapy or from major gastrointestinal losses caused by drug-induced diarrhoea and/or vomiting can compromise renal function.[1] Renal damage may be subdivided into vascular, glomerular, tubular, and interstitial damage. Post-renal damage occurs when there is blockage to urinary outflow, for example, in prosthetic hypertrophy.

Drugs may be the cause of any of these processes leading to renal failure. Analgesic nephropathy is a form of renal disease in which there is often renal papillary necrosis and a history of analgesic administration. Analgesic combinations seem to increase the risk of developing chronic tubular interstitial disease and papillary necrosis.[1] Table 1 gives examples of such drugs.

Chronic renal disease occurs as a result of primary renal disease or a renal complication of another disease, for example diabetes mellitus. As the kidney function declines, the regulatory capacity of the kidney fails and uraemic complications occur affecting most systems of the body.[2]

1. Patients with renal disease are prone to the anaemia that may result from uraemia and reduced erythropoietin production. Uraemia increases the risk of GI bleeding.
2. Another complication is that as renal function decreases, phosphate filtration in kidney is reduced, leading to high phosphate levels (which causes itching). The latter results in low plasma calcium. A lack of active vitamin D causes reduction in calcium absorption from the gut and also results in low plasma calcium. Low calcium levels stimulate PTH secretion thus releasing calcium from bones causing renal osteodystrophy.

Table 1: Drugs affecting renal function[1]

	Pre-renal disease	Drugs causing crystalluria	Analgesic nephropathy	Drugs causing glomerulonephritis	Tubulotoxic drugs	Drugs causing interstitial nephritis
Acetazolamide		X				
Aciclovir					X	
Allopurinol				X		X
Aminoglycosides					X	
Aminosalicylates						X
Amphotericin					X	
Antihypertensives	X					
Bumetanide, Furosemide						X
Caffeine			X			
Cephalosporins						X
Ciclosporin A					X	
Cimetidine						X
Cisplatin					X	
Cotrimoxazole						X
Diuretics	X					
Gold				X		X
Halothane				X		
Hydralazine				X		
Ifosfamide					X	
Indinavir		X				
Interferon						X
Isoniazid						X
Laxatives	X					
Lithium					X	X
Mannitol					X	
Mercaptopurine		X				
Methotrexate		X				
Nitrofurantoin		X				
NSAIDs	X			X	X	X
Paracetamol			X		X	
Penicillin				X		X
Pentamidine		X				
Phenytoin						X
Probenecid				X		
Quinidine				X		
Quinolones						X
Rifampicin				X		X
Salicylates			X			
Sulphonamides		X				X
Tacrolimus					X	
Thiazides				X		X
Vancomycin					X	
Vasoconstrictors	X					
Vitamin C		X				

3. Oedema results from sodium and water retention. Low serum albumin is common in renal patients and can contribute to fluid retention.
4. The kidney's role in monitoring the correct ionic, osmotic, pH and fluid balance is disturbed and control of potassium levels deteriorates. Hyperkalaemia can cause muscle weakness, arrhythmias and cardiac arrest.
5. Acidosis results from hydrogen ion accumulation manifesting itself as decreased bicarbonate levels.
6. Restless legs, pruritus (due to high phosphate levels or uraemia), nausea (accumulation of toxins) are other complications.

The use of drugs in patients with reduced renal failure can cause problems.

1. The failure to excrete a drug or its metabolites may produce toxicity. Most systemically administered drugs are eliminated at least partly by the kidney, even if it is only a tiny proportion of the administered dose. However for some drugs, the kidney is the major site of elimination of unchanged drug and these are particularly liable to require careful dose adjustment in renal dysfunction to prevent accumulation. Examples of such drugs include aciclovir, cefotaxime, ciprofloxacin, digoxin, electrolytes, fluconazole, gentamicin, lithium, meropenem, pamidronate, methotrexate and vancomycin.[3]
2. There are drugs with therapeutic activity at least partly dependent upon metabolites that are excreted unchanged by the kidney.[3] An examples of such a drug is allopurinol, whose therapeutic activity depends on the metabolite oxipurinol, the latter being excreted unchanged by the kidney.[3]
3. Nephrotoxic drugs must be avoided.
4. Sensitivity to some drugs is increased even if elimination is unimpaired. Uraemic patients are more susceptible to drug effects, for example an increased CNS-depressant effect due to increased permeability of blood brain barrier.[3]
5. Gastrointestinal disturbances are very common and prescribing antacids must be done with caution.[4]
6. Some drugs may cease to be effective when renal failure is reduced. In the presence of oedema and ascites, there is an increased apparent volume of distribution of highly water-soluble drugs. Higher doses may be needed. Conversely dehydration or muscle wasting may result in unexpectedly high plasma concentrations of drug.[3] Thus since oedema is a result of sodium and water retention, the sodium content of drugs must be checked before prescribing the drug.
7. Highly protein-bound drugs must be used with caution. This is because plasma protein binding is decreased in uraemia due to decreased plasma albumin levels allowing more free drug available at the site of action but a shorter half-life since more free drug can be metabolized and/or excreted.[3]

Besides the problems mentioned, some precautions must also be kept in mind.

1. If even mild renal impairment is considered likely on clinical grounds, renal function should be checked before prescribing any drug that requires dose modification.
2. Before starting a drug for a patient who is on dialysis, it must be checked whether the drug is dialysed or not. Sometimes doses may need to be titrated.
3. Renal function generally declines with age and many elderly patients have a glomerular filtration rate (GFR) of less than 50mL/min, which because of reduced muscle mass, may not be reflected by an elevated creatinine. Thus one can assume mild renal impairment in the elderly.[5]

Consequently, when choosing a drug for a renally impaired patient, one must also keep the above points in mind together with the complications that arise in chronic renal failure.

Principles of dosage adjustment

For toxic drugs with a small safety margin, dosage regimens based on glomerular filtration rate should be used. For those drugs where both efficacy and toxicity are closely related to plasma concentrations, the recommended regimens should be seen only as a guide to initial treatment; subsequent treatment must be adjusted according to clinical response and plasma concentration.

The total daily maintenance dose may need to be reduced and this is done by either reducing the size of the dose itself or by increasing the dosage interval. For some drugs, if the size of the maintenance dose is reduced, it will be important to give a loading dose if an immediate effect is required. When a patient is given a regular dose, it takes more than five times the half-life to achieve steady state plasma concentrations. The plasma half-life of drugs excreted by the kidney is prolonged in renal failure and so the reduced dose may take many days to achieve a therapeutic plasma concentration. The loading dose should usually be the same size as the initial dose of a patient with normal renal function.[6]

Calculating creatinine clearance

The severity of renal impairment is expressed in terms of glomerular filtration rate and is usually measured by the creatinine clearance. The equation generally quoted to calculate creatinine clearance is the Cockcroft & Gault equation and uses serum creatinine. Using serum creatinine to calculate creatinine clearance assumes that renal function and serum creatinine are stable.

CrCl= F x (140 - age) x (weight in Kg) / plasma creatinine (micromol/L)[3,4]

where F = 1.04 in females and 1.23 in males.

In cases of obesity, oedematous patients and patients with ascites, the ideal body weight must be used. The equation cannot be used in children, pregnancy, marked catabolism or rapidly changing renal function,

while in patients with muscle wasting diseases, use of the equation will lead to an overestimation of the creatinine clearance.

Drug dosing in renal replacement therapies

When prescribing a drug for a patient on a renal replacement therapy, one must be aware of the factors involved which will affect the clearance of the drug and whether a drug is actually dialysed or not. The summary of product characteristics, which is the detailed product information supplied by the drug marketing authorization holder, usually contains details of dosage regimens according to the type of replacement therapy the patient is on. Clearance of the drug may be affected by factors such as drug characteristics and dialysis characteristics. Highly protein bound drugs and very large molecules are less likely to be removed. Dialysis solutions are aqueous so water-soluble drugs are preferentially eliminated. Lipid-soluble drugs tend to have larger volumes of distribution and so concentrations in plasma are comparatively small.[3] Dialysis characteristics such as flow rate, composition of dialysate, type of dialyser membrane and duration of procedure all affect drug removal.[7]

No renal replacement therapy is as effective as the normal kidney, so the doses used will never be larger than those recommended in normal renal function. Drugs usually excreted by the kidney are usually dialysed, and vice versa, although there are some anomalies.[3] If a patient is on haemodialysis, it should be aimed towards administering the drugs after any session of dialysis since they may be removed before they even have time to act fully.

In conclusion, one must first gather the relevant information about the patient including weight of patient, medical condition, medications, replacement therapy, serum creatinine levels. A full picture of the patient's condition is important so as not to overlook any factors that may influence one's decision in choosing a drug or altering its dose.

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