"drug therapy in the patient with renal impairment"

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Introduction: The kidney suffers a triple pharmacological relationship to drugs: the first is the renal damage as a direct effect of such drugs as phenacetin and heavy metals. In such cases the area of greatest damage is the papillary region of the renal medulla by reason of the highest drug concentration and lowest oxygen tension found here. The second type of damage may result from hypersensitivity to certain drugs while the third pharmacological relation is the accumulation of drugs in the blood especially those whose active form is principally excreted by the kidney in cases where the kidney is becoming insufficient. This build-up of active drug leads to varied side-effects including nephrotoxicity and further renal impairment. Cardiac glycosides, diuretics, antihypertensives, antibiotics, sedatives and analgesics and hypoglycaemic agents are a few and perhaps among the commonest of the many drugs which it may be essential to administer to the patient with renal insufficiency or overt failure.

To start with cardiac glycosides it has been shown using tritiated digitoxin, that the effect of renal failure on digitoxin is essentially reversible on stopping the drug. Frusemide and Ethacrynic acid are highly effective in treating the oedema associated with renal insufficiency. Frusemide is not only very powerful but it has proven clinically superior to thiazides in achieving diuresis in hypoalbuminaemic states and in states of severely depressed glomerular filtration rate (e.g. creatinine clearance of 10-20 ml/min). Doses ranging from 80 mg/day to several hundred mg may be employed until an effective diuresis results; frusemide therapy results in little or no change in renal function unless acute volume depletion occurs. Still hyperuricaemia, hyperglycaemia and pancreatitis have been reported with thiazides and frusemide. Ototoxicity and profound electrolyte disturbances may occur with high doses of frusemide. Spironolactone usefully added to a thiazide diuretic in cases of refractory oedema, inhibits the tubular exchange of sodium for potassium and must therefore be cautiously administered in renal insufficiency since hyperkalaemia may occur.

In both benign and malignant hypertension, renal impairment can be prevented or delayed by effective antihypertensive therapy. With both debrisoquine and reserpine caution should be exercised when treating hypertensive patients with renal insufficiency since they may adjust poorly to lowered blood pressure levels. Methyl­dopa is largely excreted by the kidney. Therefore patients with impaired renal function may respond to smaller doses of the drug than patients with normal kidney function. In hypertensive patients with normal kidneys who are treated with hydralazine, there is evidence of increased renal blood flow; in some cases improved renal function has been noted where control values were less than normal prior to such therapy. However, as with any antihypertensive agent, hydralazine should be used with care in patients with advanced renal damage. Guanethidine may be effective in renal hypertension, including that secondary to pyelonephritis, glomerulonephritis and renal amyloidosis. Hypertension secondary to constriction of the renal artery has been treated symptomatically with guanethidine with good effect. Still cautious administration is imperative in cases of renal disease with high blood urea levels since the decreased blood pressure may further compromise renal function.

Antibiotics in relation to the kidney can be divided into those which are potentially nephrotoxic and those which become nephrotoxic in renal impairment unless the dose is adjusted: the full loading dose is administered but the
maintenance dose is curtailed to the degree of insufficiency. Considerable overlap exists between these two broad divisions.

Penicillin is rapidly inactivated, so that cumulative toxic effects occur only with doses over 10 million units per day in cases of severe renal impairment. These include neurotoxicity, muscular hyperirritability, generalized convulsions and hallucinations. As 10 million units of potassium penicillin G contain about 17 mEq. of potassium, very high doses of penicillin should be avoided in the anuric patient. Ampicillin therapy in such patients is relatively safe and renal function deterioration and an increase in the incidence of side effects only occur with doses in excess of 500 mg 6 hourly. Similarly methicillin and cloxacillin dosages need only be adjusted in very severe cases of renal impairment. High doses of carbenicillin in patients with renal impairment may lead to bleeding disorders.

Tetracycline excretion is markedly delayed in cases where the creatinine clearance is less than 30 ml/min and then the dose must be re-adjusted. Besides being nephrotoxic tetracycline accumulation may interfere with protein synthesis resulting in an increase in nitrogenous load for renal excretion. It may precipitate uraemia, hyperphosphataemia and acidosis in renal insufficiency. These changes are usually reversible.

Kanamycin is liable to cause nephrotoxicity in states of renal impairment. This, unlike ototoxicity, which if it occurs is usually bilateral and irreversible is reversible a few weeks after the drug is stopped. Advanced age and previous administration of ototoxic drugs constitute a significant predisposition. With streptomycin ototoxicity is well known to occur especially with the higher doses in patients over 40 years of age. This is especially so when renal impairment occurs. Dehydration and/or hypotension in addition to high blood levels predispose to ototoxicity and some cases of uraemia. This drug can often be avoided in patients with renal malfunction. Gentamycin excretion is virtually wholly via the kidneys and the maintenance dose must be adjusted in accordance with the glomerular filtration rate. Both nephro and ototoxicity which may complicate therapy in such cases are reversible on withdrawal of the drug. The serum half-life of erythromycin is only slightly prolonged in the anuric patient so that extrarenal factors must play a role in ridding the body of the drug. It appears relatively safe to prescribe erythromycin in the usual therapeutic dosage in those patients with renal impairment.

With reference to cephalosporins, while cephalothin requires little adjustment except in the worst cases of renal impairment (due to its very low toxicity), cephaloridin has been associated with both acute renal failure and impaired renal function in patients on the recommended doses. Though these side-effects are reversible it follows that significant dosage changes are required in cases of renal malfunction. The same applies to cephalaxin which can be removed by haemodialysis.

The possibility of bone marrow depression as a side-effect of Chloramphenicol and the availability of less toxic antibiotics has decreased the use of this drug in urinary tract infections considerably. Where serious infections require its use in patients with severe renal insufficiency no dosage adjustment is required (as the half-life of the active form of the drug is not increased) except in cases of concomitant liver disease or in the newborn where the rate of change of this antibiotic to its glucuronide is slower than normal.

While with nitrofurantoin potentially toxic serum levels may be reached in uremic patients, in the case of nalidixic acid high urine concentrations can still be achieved in the presence of a creatinine clearance of less than 30 ml/min. Therefore in patients with poor kidney function higher doses should be given initially to achieve a high serum concentration early and then use a maintenance dose after 2 or 3 days.

Polymyxin B is slowly excreted into the urine; therefore if parenteral therapy is repeated more frequently than twice daily drug accumulation may occur even with normal renal function. It also follows that renal disorders would facilitate nephrotoxicity and neurotoxic symptoms consequent on high blood levels of the drug. It is recommended that patients with such trouble be given less than 1 - 2 mg/kg body wt./day. The same argument holds for colistin.

Amphotericin B is very nephrotoxic. Even in patients with normal renal function it has been reported to decrease renal plasma flow and glomerular filtration, to impair the concentrating power, produce urinary potassium loss with consequent hypokalaemia and hydrogen-ion retention; renal tubular acidosis may supervene. Not only is there a reduction in dosage called for in the face of renal impairment but also frequent renal function, electrolyte and acid base evaluation is indicated during the term of therapy.

Sulphonamides should be avoided in renal insufficiency states because of the danger of crystal precipitation in the renal tubules which is more likely to occur as a result of diminished urinary output. Whenever these drugs are used a good urine output should be ensured. Sodium sulphadimidine in particular has been used in renal impairment since effective urinary and blood concentrations are obtained without much drug accumulation.

Hypnotics and sedatives are useful in combating the insomnia and restlessness that are often manifest in patients with renal failure. While chloral hydrate, the shorter acting barbiturates and diazepam can be given in the usual doses, long-acting barbiturates, chlordiazepoxide and the phenothiazines must be cautiously used, the latter mainly because of individual variation in metabolising the drug. It is necessary to distinguish the shorter from the longer acting barbiturates because while the former are
largely metabolised by the liver, the latter are mostly excreted by the kidneys.

No ideal drug is available as yet to combat the nausea and vomiting of the uraemic patients. Prochlorperazine is effective and can be used in some cases. In the usual doses. Occasionally these symptoms respond well to small doses of diphenhydramine (Benadryl). This is also useful in the patient with uraemic pruritus. Oral hypoglycaemic agents are best avoided. Otherwise reduced dosage schemes are advised for patients with chronic renal insufficiency as profound hypoglycaemia may result due to an increased duration of action. Phenformin may also lead to lactic acidosis in such patients.

Salicylates are to be avoided in the uraemic patient; renal excretion is erratic and gastrointestinal irritation may worsen the bleeding directly associated with uraemia. Platelet adhesiveness is also affected. Dextropropoxyphene (Doloxene) has been used in patients with renal insufficiency. The drug is chemically close to methadone but is both less analgesic and habit forming. Its analgesic power is equivalent to that of codeine. As it is metabolized primarily by the liver it may be given in therapeutic doses to these patients without significant side effects. Other drugs which have been used in patients with renal insufficiency without untoward effects include indomethacin (but not phenylbutazone), allopurinol in primary gout or in the rarer secondary gout, diphenylhydantoin in the treatment of convulsions and amitryptiline and imipramine in depressive states.

It must in conclusion, be emphasised that side-effects of drug therapy in patients with renal impairment are both more likely and more long-lasting when they occur. The seriousness of such a possible issue demands more cautious prescription and administration in such cases.

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