Today's Treatment

Diseases of the urinary system

Drug-induced renal disorders: I

J R CURTIS

British Medical Journal, 1977, 2, 242-244

The kidneys are vulnerable to damage by drugs for several reasons. These include their large blood supply, the possible concentration of drugs and their metabolites in the medullary region of the kidneys, and the high drug concentrations in renal tubular cells as a result of passive and active tubular handling of many drugs. Decreased elimination of drugs may occur owing to pre-existing renal failure resulting in the accumulation of potentially toxic drugs. Many nephrotoxic reactions are dose dependent and often occur against a background of underlying renal disease and failure resulting in further deterioration of renal function. Hypersensitivity reactions may occur with an associated vasculitis, which often affects other organs as well as the kidneys. These hypersensitivity reactions are not related to dose.

Nephrotoxic reactions due to drugs produce various histopathological appearances and functional abnormalities and present clinically in many ways (acute or chronic renal failure, systemic lupus erythematosus (SLE) syndrome, nephrotic syndrome, renal tubular syndromes, etc). Some drugs may also produce various disorders of fluid and electrolyte balance and metabolism, some of which may in their turn have a nephrotoxic effect, such as potassium deficiency due to diuretics. The question of drug-induced cancer of the urinary tract must also be considered.

Some drugs may cause difficulties in the diagnosis of renal disorders in other ways. This may be because of abnormal discoloration of the urine as a result of the excretion of the drug or its metabolites in the urine (the red colour due to phenindione and the reddish orange colour due to pyridium may be confused with haematuria). Conversely, anticoagulants may precipitate bleeding and haematuria in a patient with an otherwise silent neoplasm of the urinary tract and therefore lead to early diagnosis. The green or blue urine due to taking "kidney pills" containing methylene blue (still freely available) is startling but the diagnosis is obvious. Difficulties in diagnosis may be caused by drug-induced radiological abnormalities of the urinary tract, such as a renal pseudotumour due to anticoagulant treatment (see section on urinary tract neoplasms and drugs).

I propose to discuss briefly some of the more important drug-induced disorders of the kidney. There will be little mention of other chemicals or toxic materials that are potentially nephrotoxic and to which the patient may be exposed as a result of his occupation (exposure to benzidine or β -naphthyl-

mine resulting in bladder cancer); or which may be taken in excess deliberately or by accident (poisoning with carbon tetrachloride, ethylene glycol, phenol, etc, resulting in acute tubular necrosis); or which may be taken in excess in the diet (Worcestershire sauce, causing renal stones).

Some drugs, such as amphotericin B, have to be used in life-threatening conditions, although they are potentially very nephrotoxic. Clearly, renal function must be monitored closely when such drugs are used so that nephrotoxicity and renal failure can be recognised at an early stage and their severity balanced against the clinical benefits likely to follow from the continued use of the drug.

Other drugs are particularly likely to cause hypersensitivity reactions—for example, penicillamine and gold salts—and patients taking them should have their renal function checked frequently.

Many other drugs, however, cause renal damage only occasionally, and it is not possible to monitor renal function frequently during the administration of every drug. Patients may therefore present clinically with various renal syndromes, which will be exactly similar to those due to spontaneous renal disease. The true cause of the renal syndrome will be missed unless an extremely careful drug history is always obtained. This is clearly vital in the management of such patients because withdrawal of the offending drug may often result in cure or at least amelioration, although some form of dialysis may be needed at first—for example, in acute tubular necrosis due to drugs. A careful drug history is equally important in chronic drug-induced renal disorders—for example, analgesic nephropathy. Failure to recognise this condition may result in the patient finally developing terminal irreversible renal failure for which the only treatment is maintenance dialysis or renal transplantation.

Acute drug-induced nephropathy

Muehrcke has listed more than 70 drugs that can produce acute renal failure, and in his experience of oliguric acute renal failure drugs or chemicals were incriminated in 20-25% of the cases. Drugs producing acute renal failure may produce morphological changes singly or in combination at four major sites within the kidneys—namely, the arteries, glomeruli, tubules, and the interstitium. Thus an arteritis has been caused by several drugs, including diphenylhydantoin, gold salts, penicillins, propylthiouracil, thiazides, and sulphonamides; glomerular changes including focal necrotising glomerulonephritis and a diffuse proliferative glomerulonephritis have followed the use of hydrallazine, phenylbutazone, and sulphonamides; acute tubular necrosis has occurred after a very large number and variety of drugs (aminoglycosides, ferrous sulphate, penicillin, quinine, salicylates, paracetamol, etc); and an acute interstitial nephritis has not uncommonly followed the use of sulphonamides, phenindione, methicillin, ampicillin, and rifampicin. Occasional cases of acute interstitial nephritis have followed treatment with penicillin G, thiazides, frusemide, co-trimoxazole, phenylbutazone,

phenobarbitone, diphenylhydantoin, para-aminosalicylic acid, phenazone, gold and bismuth salts, and azathioprine.

Acute interstitial nephritis is characterised by inflammatory cells infiltrating the interstitium. Tubular lesions are always present, and therefore when the cellular infiltrate is moderate it may be difficult to distinguish acute interstitial nephritis from acute tubular necrosis. Drug-induced acute interstitial nephritis is generally considered to be a hypersensitivity reaction rather than a direct toxic effect of the drug. Support for this hypothesis includes other evidence of a hypersensitivity reaction such as rashes, fever, arthropathy, eosinophilia, and liver disease. Circulating antibodies to the offending drug may be detected. The condition is not dose-related and may be reproduced on further exposure to the drug concerned. The precise mechanisms for this type of toxic drug reaction are not clear but may involve both humoral and cell-mediated immunological responses. In some drug-induced cases of acute interstitial nephritis, antibodies have reacted with tubular basement membrane antigens. Reaginic antibodies may be implicated in some cases that have been associated with raised serum IgE concentrations or the presence of IgE-containing plasma cells in the interstitium. Clinical management includes withdrawing the suspected drug. Acute haemodialysis or peritoneal dialysis may be needed to tide the patient over a period of acute renal failure. Drug-induced interstitial nephritis has apparently responded to large doses of steroids such as prednisone or methylprednisolone in some reported cases.

DRUGS USED IN TREATING INFECTIONS

Sulphonamides

There was a considerable risk of crystal formation in the renal tubules, pelves, and ureters with some of the early members of this group of drugs—for instance, sulphathiazole—which sometimes resulted in an obstructive nephropathy with acute renal failure. Crystalluria has also occurred after treatment with acetazolamide (a sulphonamide derivative), which is used in managing glaucoma.

A hypersensitivity reaction with an acute interstitial nephritis or glomerulonephritis sometimes associated with tubular damage may also occur and cause acute renal failure. This type of reaction has been particularly associated with the long-acting sulphonamides such as sulphamethoxypyridazine, sulphamethoxydiazine, and sulphadimethoxine and has also been reported after sulphamerazine.

Sulphonamides have caused polyarteritis nodosa in some patients, and presumably some form of hypersensitivity reaction is implicated. They are occasionally responsible for activating SLE.

If a sulphonamide is to be prescribed it would seem prudent to limit the choice to one of the following, in which the risk of crystalluria or a hypersensitivity reaction seems to be minimal—sulphadimidine, sulphamethizole, sulphafurazole, and sulphamethoxazole (present in Septrin and Bactrim).

Penicillins

The penicillins are relatively non-toxic but hypersensitivity reactions with acute interstitial nephritis have occurred occasionally. Methicillin seems to be incriminated more often than other members of this group of drugs. The penicillins are occasionally responsible for activating SLE.

Cephalosporins

Cephaloridine is associated with considerable nephrotoxicity, particularly when used in high dosage and also with diuretics such as frusemide. Morphologically proximal tubular damage and clinically acute renal failure may be produced. Cephalothin may also be nephrotoxic, especially when used with one of the aminoglycosides such as gentamicin. Several cephalosporin derivatives have been introduced in recent years including cephaloglycin, cephalixin, cephadrine, and cephalolin, and their precise nephrotoxic potential remains to be determined. Cephalosporins should be avoided if possible when diuretics or an aminoglycoside are also being taken.

Tetracyclines

Tetracyclines have several potentially toxic effects. In Britain tetracycline and oxytetracycline are most commonly used. Toxic

effects are usually seen in patients with known or unsuspected chronic renal failure who are given normal doses of these drugs. Both tetracycline and oxytetracycline depend considerably for their elimination on renal excretion, and therefore in the presence of renal failure the serum half times are grossly prolonged. These drugs will therefore accumulate if normal doses are given in these conditions. Gastro-intestinal side effects, including anorexia, nausea, vomiting, and diarrhoea, are likely to occur and will lead to saline depletion with consequent progressive and sometimes rapid worsening of the renal failure.

In addition, the antianabolic effect of the tetracyclines inhibits the incorporation of amino-acids into protein and causes a rise in the blood urea concentration, a negative nitrogen balance, and an increased urinary excretion of sodium (unexplained). The end result is that severe and sometimes fatal uraemia may be produced. There is one exception to this. Doxycycline has the same serum half life in anephric patients as in normal patients, and its antianabolic effects are minimal. It may therefore be given in normal doses (100 mg once a day) even to anephric patients. All other tetracyclines are contraindicated in patients with renal failure.

Three other nephrotoxic effects may be seen rarely—firstly, the reversible Fanconi-like proximal tubular disorder attributed to degradation products of tetracycline (in particular, anhydro-4-epitetracycline). The instability of earlier preparations on prolonged or incorrect storage of the drug has been attributed to the excipient used at that time—namely, citric acid. The problem does not occur now that citric acid has been replaced by lactose.

Acute renal failure has also occurred in association with the liver failure described, usually in pregnant or postpartum patients who have been given large doses of a tetracycline intravenously.

Finally, a selective impairment of renal concentrating ability has been described after treatment with demethylchlortetracycline. This effect has been used in the management of patients with the syndrome of inappropriate antidiuretic hormone secretion.

Aminoglycosides

Aminoglycosides include streptomycin, neomycin, paromomycin, kanamycin, gentamicin, tobramycin, and amikacin. All are potentially nephrotoxic and ototoxic. Proximal tubular damage is produced, and the glomerular filtration rate, renal blood flow, and renal concentrating ability may fall. Proteinuria and microscopic haematuria may occur. The nephrotoxicity is dose-related. All the aminoglycosides are largely eliminated in the urine, so that these drugs will accumulate in renal failure unless the dosage is drastically reduced. Patients with pre-existing renal failure are particularly vulnerable to further deterioration in renal function.

Because of their severe toxicity, neomycin and paromomycin are now never given systemically but are taken by mouth for sterilising the bowel before surgery, in the "blind loop" syndrome, and in hepatic precoma. Absorption from the gut is poor, but in the presence of renal failure and hepatic damage considerable blood concentrations have been found, and deafness has resulted occasionally from oral administration of these drugs.

The parenteral administration of the other aminoglycosides should be reserved for serious life-threatening infections. If they need to be given during renal failure, nomograms and formulae are available to enable the dosage to be reduced appropriately, but regular monitoring of serum drug concentrations should also be carried out whenever possible.

Polymyxins

Colistin (polymyxin E) and polymyxin B are both potentially nephrotoxic, and this effect has usually been noted in patients with underlying renal disease, although acute tubular necrosis has occasionally been reported in patients with previously normal renal function. Because of appreciable renal elimination, the dose should be reduced during renal failure. Coincidental administration of cephalothin with colistin may increase the incidence of nephrotoxicity.

Vancomycin

Vancomycin is potentially nephrotoxic and may produce a fall in glomerular filtration rate associated with proteinuria and an increased excretion of casts in the urine.

Rifampicin

There are several reports of acute renal failure after using rifampicin. The mechanism in many cases seems to be acute tubular necrosis, but some examples show a hypersensitivity reaction with the development of high levels of antibodies to rifampicin in the serum and the presence of an acute interstitial nephritis, sometimes combined with acute tubular necrosis.

Bacitracin

Bacitracin is nephrotoxic and results in renal tubular damage associated with a fall in the glomerular filtration rate and renal blood flow together with proteinuria, an increased excretion of casts, and, rarely, haematuria. It is too toxic for systemic use but is available for local application to wounds (Polybactrin Spray, Rikospray) and also for bladder irrigation (Polybactrin Soluble GU). It is combined with polymyxin B and neomycin in all these preparations. Appreciable blood concentrations can be achieved if large amounts are applied to body surfaces or introduced into body cavities such as the peritoneal cavity or bladder. Caution is therefore indicated, particularly in patients with underlying renal disease.

Amphotericin B

Amphotericin B, an antifungal agent used to treat systemic mycoses, may produce severe renal damage with both proximal and distal tubular lesions. Renal tubular acidosis, nephrocalcinosis, hypokalaemia, impaired renal concentrating ability, together with a fall in glomerular filtration rate, and renal blood flow may all develop. Careful monitoring of renal function is needed when using this drug.

Anthelmintics

Tetrachloroethylene, still used to treat hookworm infestations, is much less toxic than carbon tetrachloride, but it has been incriminated occasionally as a cause of acute tubular necrosis.

Bismuth

Bismuth in indigestion mixtures or tablets has occasionally been taken deliberately in excessive amounts. Significant absorption may occur and has rarely caused proximal renal tubular damage and acute renal failure.

Anticoagulants

Phenindione may produce a hypersensitivity reaction associated with an acute interstitial nephritis or glomerulonephritis and resulting in acute renal failure. Anticoagulants generally can also produce acute renal failure as a result of bleeding with haematuria leading to an obstructive nephropathy due to blood clots or to external ureteric obstruction as the result of a large retroperitoneal haemorrhage.

Phenylbutazone

Phenylbutazone may produce a hypersensitivity reaction with an acute interstitial nephritis and acute renal failure.

Thiazide diuretics

Thiazide diuretics can produce acute renal failure in two ways—firstly, from over-enthusiastic use producing saline depletion and hypovolaemia and also, occasionally, by a hypersensitivity reaction with an acute renal necrotising angiitis, glomerulonephritis, and acute interstitial nephritis.

Anaesthetic agents

Methoxyflurane, a volatile anaesthetic agent, is partly metabolised in the liver. One of the metabolites is the fluoride ion, and this may

be responsible for its occasional nephrotoxicity, which is associated with distal tubular damage and acute renal failure, characterised clinically by a non-oliguric course. Histopathologically, there is an interstitial nephritis with heavy deposition of calcium oxalate crystals. In milder cases the renal concentrating defect alone occurs, producing a "renal diabetes insipidus," which may recover slowly. A similar nephrotoxic reaction has been reported in at least one patient after halothane anaesthesia.

RADIOLOGICAL CONTRAST MEDIA

Radiological contrast media may occasionally cause acute renal failure. Important factors include the chemical nature of the agent used—for instance, bunamiodyl was particularly nephrotoxic and has been withdrawn—the local concentration of the agent in the kidneys—for instance, higher concentrations are present in the renal arteries during abdominal aortography and renal angiography, and these techniques have a greater risk of nephrotoxicity—renal and hepatic function; the state of hydration; and the uricosuric effect of some contrast media—for example, iopanoic acid and meglumine iodipamide.

In the past this complication has usually followed oral cholecystography with bunamiodyl or iopanoic acid. With modern contrast media acute renal failure is rare, even when high doses are given during intravenous pyelography. Acute renal failure is a recognised hazard after intravenous pyelography in patients with myelomatosis and Bence Jones proteinuria, however, but it is now considered that the preceding dehydration is more important than the contrast medium. Fluid deprivation and purgation is a routine preliminary before intravenous pyelography, but these preliminaries are contraindicated during renal failure because the saline depletion may result in rapid worsening of the renal failure. Fluid deprivation and purgation must also be avoided in patients with diabetes mellitus and patients with myelomatosis. Acute renal failure remains a small but definite hazard after abdominal aortography and renal angiography. In a review of more than 13 000 patients having abdominal aortography, 12 patients died in acute oliguric renal failure and 27 had reversible acute renal failure.

LOW MOLECULAR WEIGHT DEXTRANS

Low molecular weight dextrans do not appear to be nephrotoxic if given in recommended doses to patients with normal hydration and normal renal function. Acute renal failure may be precipitated, however, in patients with hypovolaemia or shock if low molecular weight dextrans are given in excess. The renal tubular cells become grossly swollen with vacuoles containing dextrans. This effect has been referred to as "osmotic nephrosis."

CLOFIBRATE

Clofibrate can produce an acute toxic myopathy in patients with the nephrotic syndrome and in patients with chronic renal failure. The mechanism includes increased concentration of the free drug in the plasma due to reduced numbers of binding sites in hypoproteinaemia and to a combination of reduced protein binding (with normal plasma protein concentrations) and reduced excretion in chronic renal failure. In addition, the acute myopathy may be associated with an acute deterioration in residual renal function in those with chronic renal failure. This is probably due to salt depletion as a result of associated vomiting. Clofibrate should therefore be avoided in patients with renal failure and in the nephrotic syndrome.

Why is oral polio vaccine given to pregnant women? Is it for the benefit of the mother or the baby?

Polio vaccine virus acts locally by stimulating intestinal immunity and will not reach the fetus transplacentally. It is clearly sensible to use the opportunity of antenatal contact to immunise non-immune mothers for their own sake. The only benefit to the baby will be that if his mother is immune he cannot catch poliomyelitis from his most intimate contact after birth (although if the mother happens to receive immunisation near the end of pregnancy she might pass on one vaccine virus strain to her newborn child).