Today's Treatment

Diseases of the urinary system

Drug-induced renal disorders: II

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Apart from acute nephropathy (see part I), drugs may induce a wide variety of other conditions that affect the kidney.

Drug-induced erythematous lupus

Many drugs may produce a syndrome closely resembling spontaneous systemic lupus erythematosus (SLE). Those most commonly implicated are hydralazine, isoniazid, and procainamide. Drugs less commonly implicated include the following:

- **Antimicrobials**: sulphonamides, penicillins, tetracycline, streptomycin, and para-amino salicylic acid;
- **Antihypertensives**: reserpine and methyldopa;
- **Anticonvulsants**: ethosuximide; and propranolol;
- **Miscellaneous drugs**: griseofulvin, phenytoin, and pronethalol.

The mechanism of drug-induced SLE is not clear, but genetic predisposition may be important. Hydralazine, isoniazid, and some sulphonamides are metabolised by acetylation in the liver. The rate of acetylation by the enzyme acetylation transferase is genetically controlled; some people are "slow" acetylators and others "fast." Drug-induced SLE develops more commonly in phenotypically slow acetylators of hydralazine and antinuclear function is more commonly found in slow acetylators of isoniazid.

Clinically, the renal involvement is usually less common in drug-induced as opposed to the spontaneous form of SLE. About two-thirds of patients with spontaneous SLE have renal disease, but the incidence falls to about 20% in hydralazine-induced SLE and to about 2% in procainamide-induced SLE. Drug-induced SLE may be reversible on withdrawal of the drug, but this is not always so.

Drug-induced nephrotic syndrome

Several unrelated drugs can produce a nephrotic syndrome, which is usually but not always reversible on withdrawing the offending drug. These include inorganic and organic mercury, gold salts, penicillamine, paracetamol, tropolone, tolbutamide, perchlorate, probenecid, and phenindione.

The mechanism of drug-induced nephrotic syndrome seems to vary. With penicillamine, however, fluorescence microscopy has disclosed deposits of immunoglobulins and complement components along the glomerular capillary basement membranes, suggesting that the underlying mechanism includes deposition of immune complexes with the drug presumably acting as a hapten. Similar changes have been reported in some cases of gold-induced nephrotic syndrome while others have shown tubular damage with no evidence of immune complex deposition in the glomeruli, suggesting that in some cases at least gold has a direct toxic effect on the renal tubules. Gold salts produce various nephrotoxic effects including depression of the glomerular filtration rate, sometimes resulting in uraemia.

Drug-induced retroperitoneal fibrosis

Drug-induced retroperitoneal fibrosis is a curious condition in which extensive and progressive fibrosis occurs most commonly in the retroperitoneal space affecting and obstructing the ureters with a resulting obstructive uropathy, which may cause acute or chronic renal failure. The ureteric obstruction is due to replacement of the muscular walls of the ureter by fibrous tissue, although the lumen itself is not occluded and, paradoxically perhaps, it is usually easy to pass a ureteric catheter up the obstructed ureter from the bladder. Other structures may be affected by this fibrotic process, including the inferior vena cava and aorta. In addition, the process may occasionally occur elsewhere—for instance, in the mediastinum, liver, and thyroid gland. Several drugs have been incriminated in this condition, particularly methysergide but also ergotamine, dihydroergotamine, hydralazine, dexamphetamine, and methylphenidate. In many cases, however, no particular drug can be blamed. The underlying pathological mechanism is not known.

Localised fibrosis and stricture formation in the wall of the ureters have also been attributed to chronic analgesic abuse.

Analgesic nephropathy

Analgesic nephropathy is a well-recognised form of chronic renal disease and an important cause of chronic renal failure. The basic pathological lesion is papillary necrosis. The mechanism would seem to be damage to, and occlusion of, the vas recta leading to ischaemic necrosis of the papillae. Renal tubules passing into a necrotic papilla are obstructed, and this leads to secondary atrophy of the obstructed nephrons with resulting changes in the overlying renal cortex, which have in the past been referred to as "chronic interstitial nephritis." Analgesic nephropathy is particularly prevalent in Switzerland, Scandinavia, and Australia. Phencetin has generally been regarded as the drug responsible, although most patients have taken the phenacetin with a number of other mild analgesics, particularly aspirin, codeine, amiodopyrine, and phenazone. It is therefore difficult to be sure whether it is the combination of drugs or phenacetin alone that is the cause. It is interesting that there have been only isolated reports of papillary necrosis due to chronic abuse of aspirin or paracetamol alone. Paracetamol is particularly interesting since it is the principal metabolite of phencetin. Chronic analgesic abuse is often associated with chronic laxative abuse, and the combination may be responsible for papillary necrosis. Analgesic nephropathy is dose-related, and by the time it is recognised patients have usually taken more than 2 kg of phencetin over many years and sometimes much more than this. In Britain phencetin has been obtainable only on prescription for the past few years, and it will...
be interesting to see whether the incidence of analgesic nephropathy falls as a result of this. In Scandinavia, phenacetin has been obtained only policed in small amounts since 1961, and the incidence of analgesic nephropathy has decreased.

Clinically, analgesic nephropathy may be difficult to diagnose unless every patient with chronic renal disease is questioned, sometimes repeatedly, about drug intake. The risk of taking these large amounts of analgesic mixtures are often obscure and take place against a background of psychiatric illness. Patients may often deny or fail to mention taking analgesics. A history from a close relative may be revealing. In Australia particularly there is a close relationship between analgesic nephropathy and peptic ulceration, but this has not been a feature of cases reported in Britain. The clinical syndrome may include polyuria, polydipsia, and nocturia due to a renal-concentrating defect. There may be a sodium-losing tendency, and hypertension tends to be a late complication. Attacks of include cutaneous haematuria due to squelching of necrotic papillae may occur, and there may be sterile pyuria. The plasma urate may be high for the degree of renal failure and secondary gout may occur. Many patients present with unexplained severe chronic renal failure. The intravenous pyelogram may be normal even if papillary necrosis is present but usually the kidneys are reduced in size with caliciacts. Less commonly, but diagnostically, calcified triangular papillae or detached papillae surrounded by contrast medium and lying free in the calices may be seen. The tendency for the affected papillae to calcify may be related to the fact that these patients have been uncommonly labelled as chronic pyelonephritis.

In the differential diagnosis chronic radiological pyelonephritis with calicacts and cortical scarring must be included, and there seems to be little doubt that in the past many cases of analgesic nephropathy have been incorrectly labelled as chronic pyelonephritis. Indeed, it may be difficult to distinguish between the two in advanced cases, and they may coexist. There are also other causes of papillary necrosis to be considered, including acute pyelonephritis (rarely and particularly in diabetes), obstruction of the urinary tract (especially when associated with infection), renal tuberculosis, and sickle-cell anaemia and trait.

**Drugs increasing protein breakdown**

The glucocorticoids such as hydrocortisone, prednisone, ACTH, and tetraocortin (Synacthen) can all produce an increase in protein breakdown, which results in a rise in blood urea concentration and a lesser rise in plasma creatinine concentration, particularly in patients with underlying renal failure. These drugs can all increase the degree of clinical ureaemia.

**Hypovolaemia due to saline depletion**

Hypovolaemia due to saline depletion may be produced by drugs in various ways. The drugs have characteristic side effects such as anorexia, nausea, vomiting, and diarrhoea, and all of these may result in saline depletion. This, if severe, may result in acute renal failure due to hypovolaemia, hypotension, and a reduced renal blood flow. This complication is particularly important if it occurs in patients with underlying renal failure because their urinary sodium conservation may be impaired and they are consequently more vulnerable to saline depletion. A vicious cycle may be set up, the worsening renal failure leading to further vomiting that in time results in further saline depletion, and so on.

Other substances used in cardiac distress, particularly the powerful loop diuretics such as frusemide, may also cause hypovolaemia due to excessive urinary loss of salt and water and result in acute renal failure or worsening of existing renal failure.

**Nephropathy due to potassium deficiency**

Potassium deficiency may be produced by various drugs, including laxative abuse, diuretics, prolonged steroid treatment, carbamazepine, excessive consumption of liquorice, and, rarely, breakdown products of tetracyclines, amphotericin, and massive sodium penicillin treatment. Although the correlation between plasma potassium concentrations and total body potassium is not good, symptoms do not usually arise unless the plasma potassium concentration is below 2.5 mmol/l. An initial impairment of renal concentrating ability may occur, resulting in thirst and polyuria.

There may also be muscular weakness, lethargy, depression, and constipation. With plasma potassium concentrations below 2.0 mmol/l, a generalised flaccid paralysis may occur and, rarely, tetany and respiratory failure. The myocardium becomes more sensitive to cardiac glycosides, and deaths from cardiac arrhythmias may occur if the patients are also taking digitals.

The most important long-term effect of potassium deficiency is on the kidneys. There is a characteristic tubular lesion with vacuolation of the cells of the convoluted tubule and loss of the brush border of the tubular epithelium. Initially, the selective impairment of renal concentrating ability may produce a nephrogenic diabetes insipidus. The kidneys in chronic potassium deficiency are more susceptible to infection, and chronic pyelonephritis may result. Renal failure may also develop and progress to terminal ureaemia if the potassium deficiency is not recognised and corrected in time. Clinically, severe chronic potassium deficiency leading to renal failure is most commonly seen in patients with chronic laxative abuse.

**Nephropathy due to hypercalcaemia**

Drug-induced hypercalcaemia may occur with vitamin D intoxication or abuse and in the milk-alkali syndrome. Characteristic changes occur in the renal tubes with thickening and calcification of the basement membranes. In the early stages a relatively selective impairment of renal concentrating ability may occur producing thirst and polyuria sometimes amounting to a nephrogenic diabetes insipidus. If prolonged the hypercalcaemia and hypercalciuria may cause diffuse nephrocalcinosis and progressive impairment of renal function until severe renal failure is produced. There may be an associated pruritus and a band keratopathy due to deposition of calcium in the cornea. Renal stones may also be produced.

Occasionally an acute hypercalcaemic crisis may occur (similar to that which may occur rarely in primary hyperparathyroidism) due to vitamin D poisoning or occasionally during the treatment of skeletal metastatic cancer with cancer chemotherapy. In this condition the serum calcium may rise rapidly to levels of 5 mmol/l (20 mg/100 ml) or more. Clinically there may be an initial polyuria followed by dehydration, oliguria, and acute renal failure. There may be acute abdominal symptoms with pain, recurrent vomiting, and severe constipation. Muscular weakness, drowsiness, mental confusion, and a psychosis may also develop. Unless the severe hypercalcaemia is controlled, death may follow from uraemia. Management will mean recognition of the cause and withdrawal of the offending drug (vitamin D). Acute dialysis may be needed to tide the patient over the period of acute renal failure and also to help lower the serum calcium concentration. Prednisone treatment is also effective in lowering the serum calcium concentration. Vitamin D poisoning and in the milk-alkali syndrome. Calcitonin has also been used in the management of hypercalcaemia due to vitamin D poisoning.

**Renal stones**

Calcium-containing stones may be induced by a wide variety of drugs including prolonged steroid treatment, milk-alkali syndrome due to excessive consumption of indigestion mixtures containing alkali and calcium and milk for peptic ulceration, vitamin D intoxication, treatment of skeletal metastatic cancer with cancer chemo-
Urinary tract neoplasms and drugs

Mesothelial tumours of the renal pelvis have been reported in patients with analgesic nephropathy. There is a high incidence of papilloma, carcinoma, or both, of the renal pelvis, ureter, or bladder in patients with Balkan nephropathy, and recent evidence suggests that this condition results from contamination of local foodstuffs by nephrotoxin-producing fungi (Penicillium terracoccus var cyclopium).

Occupational exposure to chemicals in the dyestuffs and rubber industry is well known to be associated with bladder cancer. 2-aminobiphenyl, mustard has been used to treat Hodgkin’s disease and leukemias and has resulted in bladder tumours.

Drug-induced radiological changes can lead to confusion in diagnosis. Thus severe intrarenal bleeding due to anticoagulants can cause renal enlargement and caliceal deformity so that the intravenous pyelographic appearance mimics that of a hypernephroma. Aminocaproic acid used in some haemorrhagic disorders can also cause a renal pseudotumour due to the presence of blood clots in the renal pelvis, which may cause obstruction and temporary loss of function.

Bibliography


ONE HUNDRED YEARS AGO

Among the causes of that kind of Bright’s disease known as granular kidney, mental anxiety and prolonged distress take a high, if not the chief, place. A middle-aged person, man or woman, will come to us complaining that he is no longer active and eager for work, but is unaccountably languid and heavy; that he has of late become liable to dyspnoea; and that, especially after mental anxiety, attacks of this dyspnoea may come on even during hours of repose. The physician will then find the flesh failing and the complexion fading, the pulse growing tense and the heart enlarging; the urine varying widely in quantity, of low gravity, and often slightly albuminous. Now, if he inquire into the preceding history of such a patient, he will very commonly find that caring care or bitter and long sorrow has set its mark upon his life. It is impossible to prove this statement by the reading of cases; my statement is one which must be tested by others, and must stand or fall by the general voice. But I may say that I am even myself surprised to find how fully my belief is borne out by the comparison of my own cases. During the last two years, I find I have made notes of thirty-five cases of granular kidney occurring in private practice, and I find a marked history of mental distress or care, or both, in twenty-four of them. As a result of such causes, indeed, I find that granular kidney follows more frequently than degeneration of the brain or spinal cord, and far more frequently than primary failure of the heart’s muscle. (British Medical Journal, 1877.)