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Sulphasalazine induced renal failure

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Abstract

Two men with longstanding ulcerative colitis who were treated with sulphasalazine for several years and who developed chronic renal failure are reported. Renal biopsy specimens showed histological changes consistent with drug induced chronic intestinal nephritis. Extensive investigation made other causes of chronic renal failure unlikely. One of these patients underwent renal transplantation, the other has impaired but stable renal function.

Case 1

A 53 year old man with total ulcerative colitis had been maintained on sulphasalazine 1 g twice a day, and was well apart from several exacerbations that required treatment with short courses of oral corticosteroids. He was not taking any other regular medication. Twenty years after onset of his colitis he complained, at routine follow up, of lethargy, nausea and anorexia, and a 2 kg weight loss. Apart from pallor, physical examination was unremarkable.

Investigations showed a haemoglobin of 6·6 g/dl with a normocytic and normochromic picture and normal serum vitamin B12, folate, and ferritin concentrations. His serum urea value was high at 29·9 mmol/l and the serum creatinine concentration was 750 μmol/l. A 24 hour urinary protein excretion was 0·4 g/l. Ultrasound scan showed two small kidneys with no obstructive features. Antinuclear antibody and immunoelectrophoresis were negative and serum C3, C4 values were normal.

A renal biopsy specimen showed changes consistent with a drug induced intestinal nephritis. The histological changes included global sclerosis of the glomeruli, fibrosis of the interstitium, and tubular atrophy with a marked lymphocytic infiltrate.

In view of the active lymphocytic infiltration he was treated with oral prednisolone and a low protein diet. The sulphasalazine was stopped. His serum creatinine fell rapidly to 320 μmol/l from a peak level of 800 μmol/l. His renal function is still impaired but stable.

Case 2

A 61 year old man with a seven year history of total ulcerative colitis treated with sulphasalazine 1 g twice a day and intermittent corticosteroids presented with lethargy, nausea, anorexia, and weight loss. On examination he was pale and unwell.

Investigations included serum sodium 139 mmol/l, potassium 4·6 mmol/l, urea 35·7 mmol/l, creatinine 973 μmol/l, and haemoglobin 6·4 g/dl (normocytic, normochromic). Ultrasound scan of the renal tract showed two small kidneys with no obstructive features.

Immunological screening included a polyclonal increase in IgG; but his immunoglobulin values were otherwise normal. Anti-nuclear antibody and C reactive protein were also normal.

Two renal biopsies were performed 18 months apart. The first specimen showed global sclerosis in all but 4 of 20 glomeruli and the surviving glomeruli were large with periglomerular fibrosis. There was extensive patchy tubular atrophy and intestitial fibrosis with hyperplasia of surviving tubules, some showing acute damage. In places there was a moderate interstitial infiltrate of mixed inflammatory cells, including eosinophils. Some small blood vessels showed intimal fibrosis. The features were those of a chronic but still active interstitial nephritis. The second biopsy specimen showed global sclerosis in all but 6 of the 18 glomeruli. The surviving glomeruli showed ischaemic damage. There was marked tubular atrophy with interstitial fibrosis and a scattering of chronic inflammatory cells. The arteries showed intimal thickening. Immunoperoxidase study showed IgM only in the sclerosed glomeruli. The features were those of a late stage of chronic interstitial nephritis, consistent with a drug induced nephritis.

This patient subsequently underwent renal transplantation with stable renal function although subsequent renal biopsy specimens have shown chronic vascular rejection.

Discussion

Sulphasalazine is a 5-aminosalicylate (5-ASA) linked by a diazo bond to the carrier sulphapyridine. It exerts its therapeutic action, primarily through the 5-ASA released by bacterial cleavage of the diazo bond in the colon. Free, but not acetylated, 5-ASA is nephrotoxic in experimental animals.[1] Free 5-ASA is acetylated both in the small intestine[2] and in the colonic epithelium.[3] The acetylation process in the small, but not in the large intestine can easily be overloaded with rapid release of 5-ASA allowing appreciable amounts of non-acetylated 5-ASA to be absorbed.[1] Since the 5-ASAs from sulphasalazine is released in the colon where rapid acetylation takes place, nephrotoxicity would not be expected.

There have been, as anticipated, few reports of nephrotoxicity associated with sulphasalazine. A review of the literature in the last 40 years has identified only one previous case report[4] of nephrotoxicity associated with sulphasalazine. This patient had taken sulphasalazine for 18 months (dose not stated) when he presented with an acute nephrotic syndrome. Renal biopsy tissue showed minimal changes of nephropathy consistent with drug toxicity. It was of interest

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that after sulphasalazine was withdrawn, 5-ASA was substituted, and his renal failure rapidly deteriorated.

While the new salicylates have been available only recently, there have already been nine cases of nephrotoxic damage reported to the Committee on Safety of Medicines,[5] although three of these patients had also received sulphasalazine at some time and two patients also had sepsis at the time of renal damage. We are aware of five other case reports from overseas reporting renal damage in association with 5-ASA.[6-10] Of these five cases, two had received both sulphasalazine and 5-ASA at or around the time of renal impairment.[6 10] The nephrotoxicity in these patients was thought to be induced by absorption of free 5-ASA from the small intestine. The mechanism is likely to be one of hypersensitivity, rather than dose related since nephrotoxicity is still very uncommon and unrelated to dose or duration of therapy.

In determining therapeutic options for patients with inflammatory bowel disease a balance has to be struck between the well recognised side effects of the sulphapyridine moiety of sulphasalazine and the occasional toxic effects such as leukopenia compared with the use of 5-ASA compounds which eliminate the well recognised side effects of sulphapyridine[11] with the small but increased risk of developing nephrotoxicity.

These two case reports are examples of an association between drug induced chronic interstitial nephritis and long term sulphasalazine ingestion. The mechanism of the renal damage in these two cases is uncertain, but might be due to overloading of acetylation in the colon following prolonged therapy and thus absorption of free 5-ASA. Despite its prolonged use in a large number of patients nephrotoxicity associated with sulphasalazine is rare.

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