Mesoralazine induced interstitial nephritis

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Abstract
5-Aminosalicylic acid (5-ASA) has structural similarities to both phenacetin and aspirin, which are known to cause 'analgesic nephropathy'. Because of the increasing use of 5-ASA, this paper draws attention to two cases of severe interstitial nephritis resulting from 5-ASA and emphasises the importance of monitoring renal functions of patients with inflammatory bowel disease who are receiving 5-ASA preparations.

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Sulphasalazine was until recently the preferred drug for many patients with inflammatory bowel disease. Because of the considerable adverse effects, probably related to the sulphapyridine component, the recent trend has been to use the active moiety of sulphasalazine, 5-aminosalicylic acid (5-ASA). 5-ASA is commercially available in the United Kingdom and the United States as mesalazine (Pentasa, 250 mg microgranules coated with ethyl cellulose as a slow release preparation, Asacol, 400 mg tablets coated with an acryl based resin, which is released in the gut when pH is above 7) and olsalazine (Dipentum 250 mg tablets where two molecules of 5-ASA are linked by an azo bond). We report two cases of severe interstitial nephritis induced by Asacol to emphasise the importance of monitoring renal functions of patients who take 5-ASA preparations.

Case reports

CASE 1
A 28 year old man with no previous medical problems was seen in the gastroenterology clinic in April 1988 with bloody diarrhoea and lower abdominal pain. Clinical examination, blood counts, urine analysis, urea, and electrolytes were normal. Flexible sigmoidoscopy showed features suggestive of mild ulcerative colitis, which was confirmed on rectal biopsy. The symptoms settled down with mesalazine (Asacol) 400 mg three times daily and hydrocortisone (Colifoam) enema. In June 1990 he had a flare up of colitis and barium enema showed mild total colitis. Asacol was increased to 800 mg three times daily and prednisolone 40 mg was started. Although he improved initially, when prednisolone was reduced the diarrhoea worsened and he was admitted for intravenous hydrocortisone. During that admission he was found to have increased urea (7 mmol) and creatinine (394 mmol/l) values. Creatinine clearance was 45 ml/minute and urine protein was 2-9 g/24 hours. Asacol was stopped. Renal ultrasound, urine microscopy, calcium anti-glomerular basement membrane antibodies (GBM), anti-nuclear antibodies (ANA), rheumatoid factor, DNA binding, anti-cardiolipin antibody, cryoglobulins, immunoglobulins, and complements were either normal or negative. His creatinine clearance remained at 49 ml/min at three months after treatment with the drug had finished and a renal biopsy performed at that stage showed severe interstitial nephritis (Figure). A trial of prednisolone 60 mg daily was given without any improvement in renal functions. At the time of reporting he had developed hypertension, which required medical treatment. The ulcerative colitis has remained quiescent without any treatment.

CASE 2
A 24 year old man without any previous medical history was seen in the gastroenterology clinic in February 1988 with a short history of bloody diarrhoea. Sigmoidoscopy showed diffuse colitis and biopsy showed ulcerative colitis. A white cell scan showed pancolitis. His renal functions showed normal electrolyte, urea (3-6 mmol), and creatinine (88 umol/l) values. He was treated with Asacol 800 mg three times daily and hydrocortisone enemas with symptomatic recovery. He was given maintenance treatment with Asacol 800 mg three times daily. He had a relapse of colitis a few months later, which required oral prednisolone. When prednisolone was withdrawn in December 1989 he had a further relapse, which was again treated with corticosteroids. His creatinine rose through the normal range and was abnormal at 153 mmol/l in August 1989 and by February 1991 had reached concentrations over 300 mmol/l when Asacol was withdrawn. He was given maintenance treatment with prednisolone 6 mg daily. His renal functions remained unchanged and in April 1991 he was admitted for renal biopsy. Clinical examination, blood counts, electrolytes, liver function tests, calcium and C reactive protein were normal. Anti-neutrophil cytoplasmic antibodies, anti-GBM, ANA, rheumatoid factor, DNA binding, anti-cardiolipin antibody, cryoglobulins, complements, and immunoglobulins were normal or negative. Urine microscopy was normal and creatinine clearance was 47 ml/min. There was only minimal proteinuria. Renal biopsy showed inflammatory infiltrates with few eosinophil, periglomerular scarring, and peritubular scarring. Immunofluorescence for IgG, IgA, IgM, and C3 were negative. The histological appearances were consistent with active chronic interstitial nephritis. He was given a
Renal biopsy specimen showing chronic severe interstitial nephritis.

trial of prednisolone 60 mg daily, but there was no improvement in renal functions. At the time of reporting his colitis is quiescent while receiving prednisolone 3 mg daily and serum creatinine stable at 280 μmol/l.

Discussion

Acute and chronic tubulointerstitial diseases are caused by a variety of agents.1 The clinical presentations depend on the type of the insult, the site and the extent of renal damage. As the histological changes are very non-specific with regard to the aetiology, the diagnosis is made on the basis of history. The chronic interstitial nephritis in our patients was probably caused by 5-ASA (mesalazine) as they did not have any other known aetiological factors and had normal renal functions before the treatment.

‘Analgesic nephropathy’ characterised by interstitial nephritis and papillary necrosis is the most common cause of drug related renal failure. Phenacetin, aspirin or salicylate compounds and non-steroidal anti-inflammatory drugs (NSAIDs) are known to cause this type of nephropathy.2-4 5-ASA has structural similarities to salicylates and phenacitin. In experimental models 5-ASA was shown to be nephrotoxic.5-7 The mechanism of renal damage caused by 5-ASA may be similar to that of salicylates, probably by causing hypoxia of renal tissues either by uncoupling oxidative phosphorylation in renal mitochondria or by inhibiting the synthesis of renal prostaglandins.4 8 High renal concentrations of salicylates also make the kidneys susceptible to oxidative damage by reducing renal glutathione concentration by inhibition of the pentose phosphate shunt.9 Our first patient (case 1) had proteinuria in the nephrotic range. Similar cases, with histological changes mainly confined to interstitium, have been previously reported in association with other NSAIDs; it has been suggested that the nephrotic syndrome in these cases may be mediated by T-lymphocyte activation.9 10

Despite the theoretical risk of microcrystallisation of sulfapyridine in the renal tubules, only few cases of renal toxicity have been reported with sulphalazine use.11 12 In the small number of published reports, renal toxicity was seen as a part of a generalised hypersensitivity reaction to the drug. Since the introduction of 5-ASA, however, five cases of renal toxicity have been published.13-17 In addition to that, the Committee on Safety of Medicines in England and Wales has released information on nine possible cases of serious nephrotoxicity (four cases of interstitial nephritis, two nephrotic syndrome, and two renal failure) between February 1988 and December 1990 (including the cases reported here).18 Two of these patients had previous allergic reaction to sulphasalazine and one had renal dysfunction while receiving the drug. The two cases reported here were not receiving sulphasalazine before treatment with mesalazine. The significant delay between the onset of renal damage after treatment with mesalazine had started and the absence of other organ dysfunction suggest that the renal toxicity was not caused by a hypersensitivity reaction.

A number of studies have shown a significant correlation between the duration, the intensity, and the total dose of analgesics consumed and the degree of renal impairment.2 3 4 8 Our patients were receiving mesalazine 800 mg three times daily for 18–24 months when they were found to have renal impairment. 5-ASA is acetylated, independent of the acetylator status, to N-acetyl-5-ASA in the wall of ileum and colon.19 5-ASA is absorbed in both the acetylated and non-acetylated form and once absorbed behaves similarly to other salicylates. Although it has been suggested that non-acetylated salicylates are less nephrotoxic,20 21 more recent studies have shown that both acetylated and non-acetylated forms of salicylate induce renal damage at similar doses.4 7 22 Under normal physiological conditions over 80% salicylate is inactivated in hepatic mitochondria to salicylate, which is not known to cause uncoupling of oxidative phosphorylation in renal mitochondria. In the kidney salicylate is filtered and secreted by proximal tubule. Passive reabsorption occurs throughout the nephron resulting in high cortical and medullary concentration compared with the plasma concentrations.8 Clearance of salicylate, possibly related to saturation of the secretory mechanism, shows a direct correlation with urine flow and negative correlation with the plasma concentration.

The absorption of 5-ASA and acetyl-5-ASA is predominantly from the small intestine.23 24 Plasma concentrations of 5-ASA and acetyl-5-ASA are higher in subjects with intact colon compared with those with ileostomy.25 The considerable individual variation in the absorption of these compounds makes it difficult to compare the published data on small group of subjects.26 Yet detection of these compounds in subjects who had only enema preparations of 5-ASA or acetyl-5-ASA suggest that significant absorption may take place in the colon.27 The absorption from small bowel and colon depend on the pH, the
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