Original Article

Mesalazine-associated interstitial nephritis

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Abstract

Background. When used for oral treatment of inflammatory bowel disease, Asacol (a coated form of mesalazine = 5-aminosalicylic acid) can cause interstitial nephritis. The spectrum of severity, frequency of occurrence and the best renal function test to detect this complication are not known. The value of immunosuppression in addition to drug withdrawal is similarly undetermined.

Methods. Four cases of interstitial nephritis which occurred in association with oral Asacol treatment are presented and a further 12 cases who received similar treatment are reviewed. Clinical trials published previously were scrutinized to assess the frequency of impaired renal function.

Results. The available evidence suggests that renal impairment of any severity may occur in up to 1 in 100 patients, but that clinically significant interstitial nephritis occurs in less than 1 in 500 patients. This is most reliably detected by an elevated serum creatinine concentration. If the diagnosis of nephrotoxicity is delayed until 18 months after commencement of medication, restoration of renal function, which is seen on withdrawal of medication alone up to 10 months, does not occur and there is no evidence to date to indicate that addition of immunosuppression confers any significant advantage at this later stage.

Conclusions. It is suggested that serum creatinine concentration should be measured each month for the first 3 months of treatment, 3-monthly for the remainder of the first year and annually thereafter. The use of concurrent immunosuppressive therapy may necessitate extension to the period of intensive monitoring. Any elevation of serum creatinine which cannot be related to a relapse of inflammatory bowel disease should prompt immediate withdrawal of Asacol and related medications and substitution of alternative therapy. Neither the lack of urinary abnormalities on routine testing nor the absence of clinical or laboratory features of drug allergy can be relied upon to rule out interstitial nephritis during oral therapy with these drugs.

Key words: mesalazine (Asacol); inflammatory bowel disease; interstitial nephritis; monitoring renal function; lack of urinary abnormalities

Introduction

Asacol is a formulation of mesalazine (= 5-aminosalicylic acid, 5-ASA). Following ingestion, release is delayed until the terminal ileum is reached as the coating of Eudragit S remains undissolved until luminal pH exceeds 7, which occurs in the colon. Asacol is as effective as sulphasalazine at induction and maintenance of remission in patients with ulcerative colitis [1–6], and the frequency of side-effects with Asacol and a closely-related compound, Claversal (mesalazine with a coating of Eudragit L which is dissolved at pH>6) is less than with sulphasalazine [1–6]. The majority of patients who experience side-effects with oral sulphasalazine find that these settle when switched to the other drugs [2,6,7]. Therefore Asacol should be a superior oral treatment to sulphasalazine in the treatment of inflammatory disease of the large bowel. However, there are two rare drug-associated complications of Asacol therapy. One is the development of worsening diarrhoea, usually bloody, within a few hours to 5 days after commencing treatment. Four cases have been described following treatment with Asacol [8,9] and four following treatment with sulphasalazine [10–12]. The second major complication is nephropathy. The aim of this paper is firstly to report four further cases of biopsy-proven interstitial nephritis in association with Asacol treatment, and secondly, to compare these with the other 12 reported cases to try to identify common features which will permit recognition of this complication at an earlier and more easily remediable stage. Sufficient information may now be available to give an estimate of the frequency with which this rare complication occurs.
Mesalazine-associated interstitial nephritis

Previous cases (see Table 1)

Twelve previously reported cases of interstitial nephritis associated with mesalazine treatment (three due to Asacol) are included (cases 1–12) [13–19], but a further five case reports (four associated with Asacol) have been excluded [20–24] as the prime role of mesalazine in the genesis of the renal failure is less clear. In relation to one of these cases where there was proven acute glandular fever [24], the association of interstitial nephritis and renal failure and a good response to steroid therapy is well described in this disease [25] and therefore the role of 5-ASA in this case is also far from clear.

Fresh cases

Case 13

A 31-year-old man with a 4-year history of pancolitis and minimal ileitis diagnosed as Crohn’s disease and who had received Asacol 1.2 g b.d. for 3 years was found to have a serum creatinine concentration of 301 μmol/l. Asacol was discontinued 3 months later, serum creatinine remained elevated at 330 μmol/l. History and physical examination were unhelpful. Reagent strip urine testing revealed a trace of protein and 1+ of blood. There was no eosinophilia, creatinine clearance was 33 ml/min and 24-h urinary protein excretion was 190 mg. Serum complement and immunoglobulin levels were normal and no autoantibodies were detected. Ultrasound examination of the kidneys was normal. Renal biopsy showed features of interstitial nephritis. Three of 33 glomeruli were completely sclerosed and the remainder showed varying degrees of periglomerular fibrosis with tuft collapse and mesangial sclerosis. Tubules in scarred areas were either atrophic and collapsed or dilated with hyaline casts. There was moderate fibrosis of the medullary interstitium. He was treated with prednisolone 45 mg daily for 6 weeks, following which his serum creatinine was 248 μmol/l and creatinine clearance 45 ml/min.

Case 14 (See Figure 1)

A 43-year-old man commenced Asacol 800 mg thrice daily for ulcerative proctitis. Oral prednisolone was added 2 months later when relapse associated with uveitis and arthropathy occurred. On further relapse 12 months after diagnosis oral sulphasalazine was substituted for Asacol, prednisolone 10 mg daily continued and hydrocortisone foam enemas (Colifoam) introduced. The development of headache led the patient to stop sulphasalazine and restart Asacol after 1 week. Two days later he was admitted to hospital with worsening fever (T = 39°C). Serum creatinine was 167 μmol/l. Rectal mucosa was erythematous. Continued rectal inflammation despite oral Asacol for 27 months led to the addition of azathioprine 100 mg daily to prednisolone 10 mg daily. A febrile episode recurred 1 month later when the patient complained of polyuria and nocturia. Urinalysis revealed 1+ of blood and protein and 25 WBC/h.p.f. and 50 RBC/h.p.f. on microscopy. Serum creatinine was 450 μmol/l, creatinine clearance 25 ml/min and 24-h proteinuria was 480 mg. WBC was 12.3 × 10⁹/l with no eosinophilia. Asacol was discontinued. Serum immunoglobulins, complement, and renal ultrasound were normal. Renal biopsy showed interstitial nephritis with global sclerosis affecting two of 17 glomeruli, and periglomerular fibrosis affecting the majority of the remainder. The patient received methylprednisolone 1 g i.v. daily for 3 days, azathioprine was increased to 150 mg, and he remained on prednisolone 20 mg daily. At 1 month serum creatinine was 358 μmol/l and at 1 year 308 μmol/l, with a creatinine clearance of 30 ml/min while continuing prednisolone 10 mg daily and azathioprine 150 mg daily.

Case 15

A 24-year-old man was treated with Asacol following a diagnosis of inflammatory bowel disease. After 8 months of treatment his creatinine was documented at 190 μmol/l and after 12 months at 234 μmol/l. Despite this he remained on Asacol. Following increased disease activity after 22 months of Asacol treatment, investigation revealed a serum creatinine of 610 μmol/l, urinalysis showed 1+ of protein and there was no blood eosinophilia. Asacol was discontinued and he was started on prednisolone 30 mg daily. Three months later his creatinine had only improved to 466 μmol/l and he was referred for renal opinion. Creatinine clearance was 17 ml/min: 24-h urinary protein excretion was 729 mg. Immunoglobulin and complement levels were normal: autoantibody screen was negative. Ultrasound examination showed bilateral smooth ‘smallish’ kidneys. Renal biopsy appearances were similar to the previous cases: nine of 80 glomeruli were completely sclerosed, and virtually all of the remainder had prominent periglomerular fibrosis and tubulitis. The patient was treated with pulsed methylprednisolone therapy (1 g i.v. for 3 successive days), azathioprine was added to his regime and oral prednisolone was continued in a dose of 20 mg daily for 3 months and then reduced to 10 mg daily. At review 27 months post-renal biopsy his serum creatinine was 354 μmol/l, he remained on prednisolone 7.5 mg daily and azathioprine 100 mg daily.

Case 16

A 30-year-old woman had presented with ulcerative colitis 10 years previously when she had a blood urea of 8.4 mmol/l: no creatinine result was recorded. She was treated initially with sulphasalazine without satisfactory control, and prednisolone 15 mg daily was added after 2 years, the dose being rapidly reduced to 5 mg daily. The patient subsequently developed iritis and then arthralgia. Asacol 800 mg b.d. was therefore substituted for sulphasalazine, at which time the patient’s blood urea was noted to be between 8 and
<table>
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<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>5-ASA and duration</th>
<th>Clinical features</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>1</td>
<td>42,M</td>
<td>UC</td>
<td>1.5 g/day 7 months</td>
<td>T = 39°C, no rash, no eosinophilia, iridocyclitis, weight loss</td>
<td>Withdrawal of 5-ASA and methylprednisolone 1 mg/kg/day led to 'normal' renal function after 1 year</td>
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<td>Urine: WBCs 25/ul</td>
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<td>Creat cl 33 ml/min</td>
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<td>U prot 400–600 mg/24 h</td>
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<td>Serum antibodies NEG; Igs NAD</td>
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<td>Renal biopsy: interstitial nephritis</td>
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<td>2</td>
<td>26,M</td>
<td>UC</td>
<td>1.2 g/day 10 months</td>
<td>Weight loss, anorexia, malaise, Polydipsia and polyuria. Creatinine 165 μmol/l</td>
<td>Withdrawal of Asacol led to recovery of renal function after 3 months</td>
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<td>Urine: blood 2+, protein 2+</td>
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<td>No renal biopsy</td>
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<td>3</td>
<td>29,M</td>
<td>UC</td>
<td>2.4 g/day 7 months</td>
<td>Polydipsia, polyuria 1 month</td>
<td>Withdrawal of 5-ASA led to recovery of renal function and after 6 weeks; creat cl 100 ml/min</td>
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<td>No eosinophilia</td>
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<td>Creatinine 210 μmol/l</td>
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<td>Urine: 50–60 WBCs/h.p.f.</td>
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<td>Creat cl 38 ml/min</td>
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<td>U prot 700 mg/24 h</td>
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<td>Renal biopsy: interstitial nephritis</td>
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<td>4</td>
<td>14,M</td>
<td>UC</td>
<td>0.75 g/day 3 years</td>
<td>Acute nephritis after higher dose</td>
<td>Withdrawal of 5-ASA led to recovery of renal function after 1 week when creat cl 89 ml/min/1.73 m²</td>
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<td>Loin pain, polydipsia, polyuria. Nocturia and haematuria. Then oliguria and oedema.</td>
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<td>Creatinine 270 μmol/l</td>
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<td>Urine: 200 RBCs/h.p.f.; 10 WBCs/h.p.f.</td>
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<td>Renal ultrasound: large kidneys</td>
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<td>No renal biopsy</td>
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<td>5</td>
<td>31,M</td>
<td>UC</td>
<td>0.5 g/day 3 years</td>
<td>Asymptomatic, no fever</td>
<td>Withdrawal of 5-ASA led to no recovery after 6 months</td>
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<td>Creatinine 380 μmol/l</td>
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<td>Cre at cl 17–21 ml/min</td>
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<td>U prot 426 mg/24 h</td>
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<td>Renal biopsy:</td>
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<td>Glomerulosclerosis</td>
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<td>Mesangial immune deposits</td>
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<td>Interstitial nephritis</td>
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<td>6</td>
<td>28,M</td>
<td>UC</td>
<td>1.2 g/day 2 years</td>
<td>Worsening diarrhoea</td>
<td>Withdrawal of Asacol led to no recovery after 3 months (creat cl 49 ml/min).</td>
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<td>2.4 g/day</td>
<td>Urine NAD</td>
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<td>Creatinine 394 μmol/l</td>
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<td>Creat cl 45 ml/min</td>
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<td>U prot 2.9 g/24 h</td>
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<td>Serum antibodies NEG; Igs NAD</td>
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<td>Renal ultrasound: normal</td>
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<td>Renal biopsy: interstitial nephritis</td>
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<td>7</td>
<td>24,M</td>
<td>UC</td>
<td>2.4 g/day 3 years</td>
<td>Initially normally creatinine</td>
<td>Withdrawal of Asacol led to no recovery and subsequent prednisolone 60 mg daily produced no improvement</td>
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<td>Creatinine 153 μmol/l at 6 months</td>
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<td>Creatinine 300 μmol/l at 3 years</td>
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<td>No eosinophilia</td>
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<td>Urine NAD</td>
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<td>Creat cl 47 ml/min</td>
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<td>U prot 'minimal'/24 h</td>
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<td>Serum antibodies NEG; Igs NAD</td>
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<td>Renal biopsy: interstitial nephritis</td>
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<td>8</td>
<td>34,M</td>
<td>UC</td>
<td>3 g/day 2 years</td>
<td>Creatinine 470 μmol/l</td>
<td>Withdrawal of Salofalk and prednisolone 5 mg daily to control UC</td>
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<td>Urine: 'A few dysmorphic RBCs'</td>
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<td>Creat cl 17 ml/min</td>
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<td>U prot 240 mg/24 h</td>
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<td>Serum antibodies: NEG</td>
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<td>Renal ultrasound: R = 8.5, L = 9.0 cm</td>
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<td>Renal biopsy: interstitial nephritis</td>
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<td>Case</td>
<td>Age</td>
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<td>Diagnosis</td>
<td>5-ASA and duration</td>
<td>Clinical features</td>
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<td>9</td>
<td>34, F</td>
<td>UC</td>
<td>1.5-2 g/day</td>
<td>10 months</td>
<td>Undefined renal disease before 5-ASA treatment (creatinine 228 μmol/l creat cl 51 ml/min)</td>
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<td>Creatinine 350 μmol/l after 10 months</td>
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<td>Urine: a few RBCs</td>
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<td>Creat cl 25 ml/min</td>
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<td>U prot 500 mg/24 h</td>
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<td>Serum antibodies NEG</td>
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<td>Renal ultrasound: R = shrunken with cyst, L = 9.0 cm</td>
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<td>Renal biopsy (L): Interstitial nephritis</td>
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<td>10</td>
<td>20, M</td>
<td>UC</td>
<td>1.5 g/day</td>
<td>3 years</td>
<td>Fever &amp; myalgia</td>
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<td>Creatinine 660 μmol/l</td>
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<td>Urine: a few WBCs</td>
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<td>Creat cl 14 ml/min, U prot 400 mg/24 h</td>
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<td>Serum antibodies NEG</td>
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<td>Renal ultrasound: normal</td>
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<td>Renal biopsy: interstitial nephritis</td>
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<td>11</td>
<td>22, M</td>
<td>UC</td>
<td>1.5 g/day</td>
<td>6 months</td>
<td>Creatinine 166 μmol/l</td>
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<td>Eosinophilia</td>
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<td>Urine: 20–50 WBCs?, WBC casts</td>
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<td>Creat cl 54 ml/min</td>
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<td>U prot 300 mg/24 h</td>
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<td>Urine: WBCs &amp; WBC casts</td>
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<td>Creatinine 165 μmol/l</td>
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<td>12</td>
<td>29, M</td>
<td>CD</td>
<td>1.5 g/day</td>
<td>8 months</td>
<td>Creatinine 426 μmol/l</td>
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<td>Eosinophilia</td>
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<td>Urine: granular casts</td>
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<td>Creat cl 21 ml/min</td>
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<td>U prot 500 mg/24 h</td>
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<td>Serum antibodies NEG; Ig's NAD</td>
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<td>Renal ultrasound: normal</td>
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<td>Renal biopsy: interstitial nephritis</td>
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<td></td>
<td>1.5 g/day</td>
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<td>Creatinine 374 μmol/l</td>
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<td>Creat cl 24 ml/min</td>
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<td>2 g/day</td>
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<td>Creatinine 616 μmol/l</td>
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<td></td>
<td>Creat cl 13 ml/min</td>
</tr>
<tr>
<td>13</td>
<td>31, M</td>
<td>CD</td>
<td>2.4 g/day</td>
<td>3.5 years</td>
<td>Asymptomatic. No eosinophilia</td>
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<td>Creatinine 301 μmol/l</td>
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<td>Urine: blood trace, protein trace</td>
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<td>Creat cl 31 ml/min</td>
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<td>U prot 190 mg/24 h</td>
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<td>Renal ultrasound: normal</td>
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<td>Renal biopsy: interstitial nephritis</td>
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<tr>
<td>14</td>
<td>43, M</td>
<td>UC</td>
<td>2.4 g/day</td>
<td>28 months</td>
<td>T = 39.4°C. No eosinophilia</td>
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<td>Creatinine 450 μmol/l</td>
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<td>Urine: protein+, blood+</td>
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<td>Creat cl 25 ml/min</td>
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<td>U prot 480 mg/24 h</td>
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<td>Renal ultrasound: normal</td>
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<td>Renal biopsy: interstitial nephritis</td>
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<tr>
<td>15</td>
<td>24, M</td>
<td>UC</td>
<td>2.4 g/day</td>
<td>22 months</td>
<td>No eosinophilia</td>
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<td>Creatinine 610 μmol/l</td>
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<td>Urine: protein+</td>
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<td>Creat cl 17 ml/min</td>
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<td>U prot 729 mg/24 h</td>
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<td>Serum antibodies NEG; Ig's NAD</td>
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<td>Renal Ultrasound: 'smallish' kidneys</td>
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<td>Renal biopsy: interstitial nephritis</td>
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</table>
CD, Crohn's disease; Creat cl, creatinine clearance; F, female, h.p.f., high-power field; Igs, immunoglobulins; IVU, intravenous urogram; M, male; NAD, nil abnormal detected; NEG, negative; RBCs, red blood cells; RRT, renal replacement therapy, U prot, urinary protein; UC, ulcerative colitis; WBCs = white blood cells.

Table 2. Classification of cases

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
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</thead>
<tbody>
<tr>
<td>Duration of 5-ASA administration (months)</td>
<td>≤10</td>
</tr>
<tr>
<td>Number of patients</td>
<td>7</td>
</tr>
<tr>
<td>Median serum creatinine concentration (range, μmol/l)</td>
<td>210 (165–426)</td>
</tr>
<tr>
<td>Number recovering renal function after drug withdrawal alone/total so treated</td>
<td>5/6</td>
</tr>
<tr>
<td>Number recovering at least some renal function after drug withdrawal and immunosuppression/total so treated</td>
<td>1/1</td>
</tr>
</tbody>
</table>

*In group B no significant difference in outcome between those having drug withdrawn alone and those having drug withdrawn and immunosuppression (P = 0.84; Fisher's exact probability test).

Classification of cases (See Table 2)

It was possible to classify the cases into those receiving 5-ASA-containing compounds up to 10 months (group A) and those receiving these drugs for 1½–3½ years (group B). When this was done an association with serum creatinine concentration and the response to withdrawal of treatment alone was apparent (Table 2). In group A, consisting of seven patients, withdrawal of the drug resulted in recovery of normal renal function in six patients (only one of these received steroids as well). In group B, stopping the drug alone produced no recovery of renal function in five of six patients and in two of these five failures, subsequent administration of high dose steroids still produced no improvement. Thus in only one of a total of three patients where both the drugs were stopped and steroids given did some recovery of renal function occur. In two further patients who received azathioprine and steroids in addition to drug withdrawal, only one achieved some recovery of renal function. Thus in group B no recovery occurred in two-thirds and only a partial recovery occurred in the remaining third. When the proportion of patients responding to drug withdrawal alone were compared with that responding to drug withdrawal and immunosuppression in group B, no statistically significant difference was found (see Table 2).
Central surveillance for renal disease

Reports to the Medicines Control Agency over 14 years include 16 cases of interstitial nephritis, two of glomerulonephritis and one of undefined nephropathy associated with Asacol treatment. These have presented as varying degrees of renal failure. Only one patient is reported to have died. Nephrotic syndrome was reported in three cases and appears to be much less common.

Discussion

Reports of Asacol-related nephrotoxicity appeared 4 years ago [26]. Cases were so limited in number that it was not possible to identify the predominant form let alone the clinical features which might lead to earlier diagnosis. On the basis of the present evidence it is now clear that the predominant and most serious renal lesion is chronic interstitial nephritis presenting with impaired renal function. Acute nephritis and minimal change nephrotic syndrome are much less common. These cases of interstitial nephritis related to Asacol therapy resemble those described in other non-steroidal anti-inflammatory drugs [27]. The lesion differs from that seen with other drug groups in that the drug may have been taken for several months before it develops. Clinical evidence of an allergic reaction is scanty and classical features of fever, rash, arthralgia and eosinophilia are uncommon. Diagnosis is usually by renal biopsy. Histological confirmation of the diagnosis was available in 14 of the 16 cases described above (Table 1). On clinical grounds, the cases fell into two groups (Table 2). The implication is that provided the diagnosis is made early enough (up to 10 months) the lesion regresses in 85% of cases and functional recovery is possible by withdrawal of the drug alone. When the diagnosis is delayed beyond 18 months, only partial recovery is likely to be achieved in just one-third of cases. In these circumstances, the value of aggressive immunosuppression in addition to drug withdrawal in these cases in order to arrest any further disease progression is unproven. Only two of five cases so treated recovered some renal function whereas those in whom drug withdrawal alone was employed, only one of six cases recovered some renal function, a statistically insignificant difference (see Table 2). This supports the view expressed previously [19] that extensive fibrosis is unlikely to be reversed by use of immunosuppressant drugs.

How may earlier diagnosis be achieved? Abnormalities on reagent strip urine testing in the 16 cases described above were scanty, even at a time when renal function was significantly impaired. Microscopic haematuria was only noted in six of the 16 cases. Although low-grade proteinuria was present in all, it was only of sufficient quantity to reach 2+ or more on reagent strip testing in two cases. Presence of white blood cells on urine microscopy was also only noted in six of the 16 cases. This reflects previous observations of patients involved in clinical trials of Asacol. No significant urinary abnormalities were found in 415 patients with inflammatory bowel disease who did not relapse given Asacol or similar medication (0.75–4.8 g/day) for between 4 weeks and 6.9 years [1–3,8,28–31]. However, in one of these studies 31 of 58 patients (53%) with ulcerative colitis taking Asacol 2.4–4.8 g/day for 24 months had pyuria (undefined) on one or more follow-up visits [29]. Three patients had a trace of proteinuria before the study which disappeared in two but persisted in the third. Two other patients developed a trace of proteinuria during the study. Based on this evidence, neither urine testing nor examination of the urinary spun deposit, a time-consuming and relatively expensive procedure, can be relied upon as an early indicator of onset of 5-ASA-related nephrotoxicity.

Experience with the estimation of urinary enzyme excretion, a more sensitive and specific method to detect tubular damage, is very limited. Of nine patients with Crohn’s disease treated with 5-ASA 500 mg thrice daily for 4–12 weeks, only one patient had an increase in enzymuria after treatment [28]. As yet, no reagent strip test for tubular damage is freely available but a method is being developed. If it proves to be sufficiently sensitive and specific it would be an ideal cheap method of screening.

Serial estimations of serum creatinine in the 415 patients who did not relapse, reported in the context of clinical trials with Asacol or similar medication and in an additional 34 patients treated with Asacol for chronic ulcerative colitis are available [1–3,6,8,28–31]. In the latter study an undefined elevation of creatinine prevented completion of 4 weeks of Asacol therapy in one patient [31]. Therefore, minor rises in serum creatinine concentration are likely to be encountered in approximately 1% of patients with inflammatory bowel disease treated with Asacol for periods exceeding 4 weeks. No serious impairment of renal function occurred in any of these patients, indicating that this occurs with a frequency less than one in 500 patients provided surveillance of serum creatinine is maintained.

One (case 11) of the 16 cases of interstitial nephritis described above had eosinophilia, and skin rash was not a feature. Only three patients had fever and one of these had an arthralgic episode. This suggests that direct hypersensitivity is not the prime mechanism and that a cell-mediated delayed hypersensitivity response is more likely. Employment of specific monoclonal antibodies to identify the composition of the cellular infiltrate in interstitial nephritis showed that the main cells were monocytes/macrophages and T-helper/inducer (CD4-positive) cells [32]. This investigation has not been undertaken in any of the present cases. The mechanism(s) whereby such apparent immune activation occurs remains speculative. In the absence of evidence taken usually to indicate drug allergy, it is possible that significant systemic absorption of mesalazine or its metabolite, N-acetyl 5-ASA, results in direct
or indirect production of patchy necrosis of tubular epithelium which evokes an immune reaction. The possible mechanisms causing this damage, both hypoxia and direct toxicity, have been considered in detail recently [18]. The same authors reviewed data indicating that absorption of mesalazine in the case of delayed or sustained release formulations of 5-ASA available in the UK (Asacol, Dipentum and Pentasa) were all much the same (20–36% of the administered dose). Although the systemic absorption of the newer rectal foam formulation of Asacol is approximately one-half of that of the oral preparation (15% versus 30% of the administered dose: SmithKline Beecham: data on file), this difference is not so great that vigilance for nephrotoxicity should be relaxed when any rectal mesalazine preparation is administered. In relation to rectal Asacol, no case of interstitial nephritis has been reported to date.

Our observations and a review of the literature suggest that as many as one in 100 patients taking therapeutic dosages of Asacol will develop some renal impairment but that this will be serious in less than one in 500 patients. When renal damage does occur, its presence is unlikely to be detected by urinalysis in its early remediable stages. It is suggested that serum creatinine should be monitored every 4 weeks during the first 3 months of therapy to identify patients who may be at risk of developing progressive renal damage. Monitoring frequency can then be reduced to 3-monthly and at the end of the first year to annually. Increased monitoring frequency is warranted in patients receiving concurrent steroid therapy since this may mask the development of significant renal damage. It is further warranted in patients receiving azathioprine which itself may cause impairment of renal function [22]. Any sustained elevation of creatinine should result in withdrawal of Asacol and related drugs. The occurrence of fever, whether associated with worsening symptoms of colitis or not, and particularly in relation to an increase of dosage, should prompt assessment of renal function by estimation of serum creatinine. If withdrawal of medication does not result in a fall in serum creatinine, then the patient should be referred for consideration of renal biopsy as only this will determine whether interstitial nephritis or glomerulonephritis associated with inflammatory bowel disease [33] is the cause of the persistently impaired renal function. As glomerulonephritis occurs with increased frequency in patients with inflammatory bowel disease, urine testing at routine out-patient follow-up visits should not be neglected. In this situation it is possible that significant urinary abnormalities may be present whilst serum creatinine levels are normal.

It is difficult to accept the view that there is no need for routine monitoring of renal function in patients taking preparations containing 5-ASA [34], when prompt withdrawal of the drug could result in restoration of normal renal function if this is depressed as a result of interstitial nephritis in its early stages. The protocol suggested by the authors to monitor serum creatinine would cost little in comparison with the cost of providing even a small number of patients with renal replacement therapy and the savings in terms of elimination of distress will be even greater. The view that renal function should be monitored routinely in patients receiving 5-ASA has been expressed before by those who have reported earlier cases [17,19,24]. Now is the time to implement this important preventive measure.

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Mesalazine-associated interstitial nephritis


Received for publication: 22.6.95
Accepted in revised form: 17.11.95