Attendance for smear test after initial letter and two reminders

	Letter only group	Appointment group	% Greater response shown by appointment group (95% confidence interval)
No (%) attending after initial letter	26/122 (21)	43/118 (36)	15 (4 to 27)
Cumulative total (%) after first reminder	34/122 (28)*	52/118 (44)	16 (4 to 28)
Cumulative total (%) after second reminder	39/122 (32)†	56/118 (47)	15 (3 to 28)
Cumulative total (%) women aged 45-54·5 after second reminder	28/74 (38)	29/61 (48)	10 (−7 to 26)
Cumulative total (%) women aged 54·5-65 years after second reminder	11/48 (23)	27/57 (47)	24 (6 to 43)

* Included two women who attended a health authority clinic.
† Included three women who attended a health authority clinic.

Comment

The overall response rate was lower than in other studies.[4] The most likely explanation is that reluctance to attend for a smear test is greatest in women who have never had one. Our results suggest, however, that middle aged women who have not had a smear test are more likely to accept an invitation to have one if the general practitioner offers a specific appointment rather than an open invitation. This was especially true for women aged 54-65. Owing to the small number of women in this study we cannot be sure about the magnitude of this difference, but it is probably at least 6% and may be as much as 43%. It has been reported that older women are less likely to attend for cervical cytology.[3] We saw this in the letter only group but not in the appointment group. Sending times of appointments is administratively more complex than sending each patient an identical letter, especially if the letters of invitation are dispatched from the family practitioner committee, which was the original plan in Nottingham. Such an appointment system would allow practices to have more control over their workload, however, and if the invitations were sent directly from the general practitioner it would allow easier updating at the last minute.

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Isolated minimal change nephropathy associated with diclofenac

Several renal changes have been associated with treatment with non-steroidal anti-inflammatory drugs.[1,2] We report two cases of isolated minimal change nephropathy after treatment with diclofenac.

Case reports

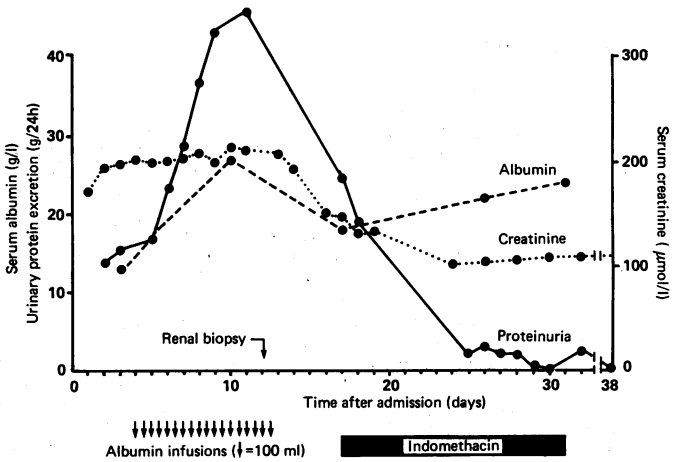
CASE 1

A 70 year old woman with hypertension had been taking atenolol, chlorthalidone, and hydralazine for more than a year. Three months before her admission diclofenac 100 mg a day had been added because of coxarthrosis. Two and a half months after diclofenac was started a dipstick test for proteinuria had yielded a negative result. Two weeks later progressive peripheral oedema and anorexia developed, prompting her to stop taking diclofenac.

On admission she had massive oedema of the legs and moderate hypertension. Serum creatinine concentration was 230 μmol/l, serum albumin concentration 13 g/l, and urinary protein excretion 14 g/24 h. Urine microscopy showed a few red and white cells and some hyaline and granular casts. No other cause of her nephrotic syndrome was found. Three weeks after she stopped taking diclofenac renal biopsy was performed. Appearances on light microscopy, immunofluorescence, and electron microscopy were compatible with a minimal change nephropathy. Symptomatic treatment was started, consisting of sodium restriction, frusemide, and albumin infusions (figure). After two and a half weeks indomethacin 100 mg a day was added. Proteinuria decreased gradually and 26 days after the renal biopsy had resolved.

CASE 2

A 56 year old woman with arthritis of the knee took diclofenac 150 mg a day for two separate periods of 13 and 20 days. After the second period she was admitted to hospital with a nephrotic syndrome. Serum creatinine concentration was 90 μmol/l, serum albumin concentration 18 g/l, and urinary protein excretion 11 g/24 h. Urine microscopy showed 15-25 leucocytes and a few erythrocytes per field; urine culture gave negative results. Further laboratory investigations showed no cause for the nephropathy. Six weeks after she stopped taking diclofenac a renal biopsy was performed. Appearances on microscopy, immunofluorescence, and electron microscopy were compatible with a minimal change nephropathy.



Serum creatinine and albumin concentrations and 24 hour urinary protein excretion after treatment with diclofenac.

Two weeks later she began treatment with prednisone 75 mg a day because conservative treatment with diuretics and salt restriction had been unsuccessful, with serum albumin concentration decreasing and her renal function deteriorating. After 14 days the dose was reduced to 10 mg a day. The proteinuria decreased gradually and was completely gone after three weeks. Proteinuria did not recur after the prednisone was stopped.

Comment

In most cases of nephrotic syndrome associated with treatment with non-steroidal anti-inflammatory drugs interstitial nephritis is found on biopsy, although tolmetin and sulindac have been associated with isolated minimal change nephropathy.[3] The clinical course in our patients suggests that diclofenac was responsible for their minimal change nephropathy. Minimal change nephropathy has been described before with diclofenac, but interstitial nephritis was also present.[4] Sampling error might account for the failure to show interstitial nephritis in our patients, but as the number of glomeruli in the biopsy specimens was 10 and 15, respectively, this was unlikely.

The pathophysiology of this adverse effect of diclofenac is unknown, but the absence of interstitial nephritis is an argument against a mechanism mediated by T cells.[5] The fact that the proteinuria resolved after indomethacin was added to treatment in case 1 argues against a pivotal role of inhibition of prostaglandin as well.

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Veno-occlusive disease of the liver secondary to ingestion of comfrey

There is currently considerable interest in alternative medicine and herbal remedies. These treatments are not without risk, however, as illustrated by the following case.

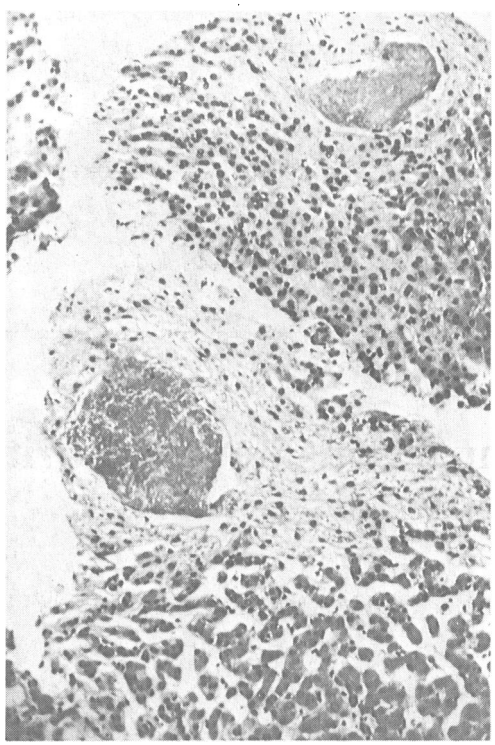
Case report

A 13 year old boy was admitted in July 1986 for investigation of hepatomegaly and ascites. Three years earlier Crohn's disease had been diagnosed from radiographs showing consistent changes in the terminal ileum and colon and from histological studies of the colon. He was treated with prednisolone and sulphasalazine with benefit. At his parents' request these drugs were discontinued and he was treated with acupuncture and comfrey root, prescribed by a naturopath. Up to 1986 he had been regularly given a herbal tea containing comfrey leaf. The exact quantities of leaves given and frequency of administration are unknown. An exacerbation of his inflammatory bowel disease in 1984 required a further course of prednisolone. In June 1986 he presented with fatigue, diarrhoea, and weight loss and a few weeks later developed fever, abdominal pain, and swelling. He was taking prednisolone and sulphasalazine. He had never taken azathioprine.

On examination he had ascites and tender hepatomegaly but no dehydration, jaundice, or heart failure and no stigmata of chronic liver disease. Sigmoidoscopy showed mildly inflamed, cobblestoned mucosa. He had mild iron deficiency anaemia (haemoglobin 117 g/l) and raised serum bilirubin concentration (26 mmol/l, normal <17) and aspartate aminotransferase activity (87 IU/l; normal 6-35). Serum albumin was low at 27 g/l. The results of the following tests were normal: urea, electrolytes, serum globulin, alkaline phosphatase, complement, plasma viscosity, full coagulation screen, autoantibody profile, and acid haemolysis. Hepatitis B surface antigen and antibodies to hepatitis A were absent as were Epstein-Barr virus and cytomegalovirus. Ascitic fluid protein concentration was 27 g/l. The inferior vena cava and major hepatic veins were patent on Doppler ultrasound and percutaneous phlebography. Percutaneous liver biopsy showed the thrombotic variant of hepatic veno-occlusive disease (figure).[1] He was treated with spironolactone, salt restriction, and bed rest with a good response. His bowel disease remained relatively inactive with treatment with prednisolone and sulphasalazine; at the time of writing he was back at school and tolerably well on his medication.

Comment

Known or suspected causes of hepatic veno-occlusive disease are systemic lupus erythematosus, alcoholic hepatitis, immune deficiency, azathioprine (in renal transplant recipients), radiotherapy, chemotherapy (especially in bone marrow transplant recipients), and pyrrolizidine alkaloids.[2] These alkaloids are present in a wide variety of plant species, and those of the genera *Heliotropium*, *Senecio*, and *Crotalaria* are particularly toxic.[3] Ingestion of plants containing alkaloids in "bush" or herbal teas or as food contaminants is responsible for appreciable numbers of cases world wide.[3] Only two cases of hepatic veno-occlusive disease as a result of pyrrolizidine alkaloid ingestion have been described in Britain, however, and both patients had ingested imported herbal teas. We think that the only possible causal factor for hepatic veno-occlusive disease in our patient was comfrey, which he had regularly ingested for two to three years; major hepatic vein thrombosis but not veno-occlusive disease has been described in patients with colitis.[1] The common comfrey, *Symphytum officinale*, a native British plant, contains at least nine potentially hepatotoxic pyrrolizidine alkaloids in its leaves and roots.[3] These alkaloids are less toxic than those in other plants—for example, senecios—which may explain why only a few cases of hepatic veno-occlusive disease caused by ingestion of comfrey are known (G Nicholson and C C J Culvenor, personal communications) and only one has been published.[4] This second published case is the first to result from a native British plant. The prognosis for our patient remains uncertain for although about half of Jamaican patients with acute hepatic veno-occlusive disease recovered completely, the remainder died or developed cirrhosis.[5] Malnutrition and poor health may be risk factors in Jamaica so our patient may have been susceptible to hepatic veno-occlusive disease from comfrey because of his underlying inflammatory bowel disease.[5]



Two freshly thrombosed centrilobular veins in liver biopsy with intimal thickening, sinusoidal distension, and loss of centrilobular hepatocytes. Haematoxylin and eosin.

This report serves as a reminder that herbal as well as orthodox medications may have serious side effects.

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