SIDE EFFECTS OF DRUGS

Liver granulomas and allopurinol

Allopurinol (4-hydroxypyrazolo (3,4-d) pyrimidine; Zyloprim) lowers serum urate concentrations by competitively inhibiting xanthine oxidase, the enzyme regulating the terminal steps in urate biosynthesis. It has been used since 1962 as an effective treatment for hyperuricaemia. The most common side effects—fever, malaise, gastrointestinal irritation, and hypersensitivity reactions affecting the skin and blood—may occur months or years after long-term administration.[1] Adverse reactions affecting the liver include hepatomegaly with reversible abnormalities in liver function values with and without jaundice,[1] massive hepatic necrosis,[2] severe hepatitis,[3] and a single reported case of granulomatous hepatitis after a one-month course of allopurinol.[4] We describe here an unusual case of widespread granulomas in the liver of a patient who had been receiving allopurinol for over six years.

Case report

A previously well 47-year-old white truck driver was admitted to hospital in October 1976 for investigation of acute abdominal pain, fever, and malaise. History revealed that he had been in a minor motor vehicle accident two weeks before onset of symptoms. He had sustained no injuries and had no symptoms over the two weeks. He did not smoke and admitted to an ethanol intake of less than 57 g (2 oz) a week. He did not abuse any other drugs. His only medication was allopurinol, 100 mg three times a day, which had been first prescribed six years earlier for asymptomatic hyperuricaemia. The drug was discontinued on admission. About 30 years earlier this man had developed a diffuse urticaria associated with pruritus after treatment with a sulphonamide drug. He did not suffer from allergic rhinitis, bronchial asthma, or other allergic manifestations. Physical examination showed an anxious, febrile man in no physical distress. Other findings on the examination were unremarkable.

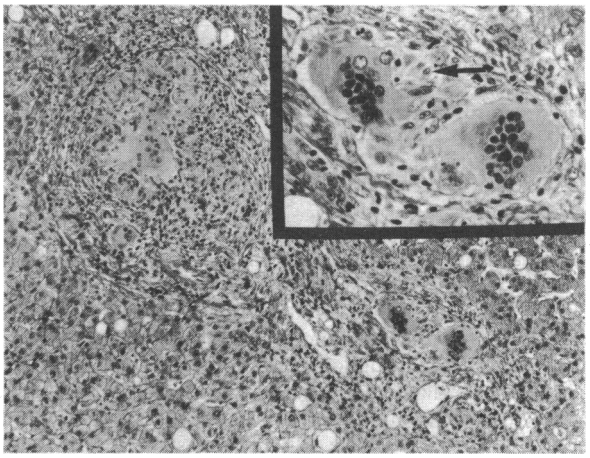
Laboratory investigations showed: white blood count (WBC) $8{\cdot}8 \times 10^9$/l with 7% eosinophils; erythrocyte sedimentation rate (ESR) 80 mm in first hour; aspartate transaminase (SGOT) 40 IU (normal 8-23 IU); and alkaline phosphatase 19 KA units (normal 3-12 KAU). Serum protein, total bilirubin, and urate concentrations were normal. His symptoms and all laboratory values improved in hospital over two weeks, and he was discharged with no specific diagnosis. After discharge, the patient resumed his allopurinol. About three weeks after allopurinol was readministered, he reported daily episodes of low-grade fever, malaise, and gastrointestinal discomfort. Initially these symptoms were mild and required no medical intervention or investigation. They became progressively more frequent and severe, however, and he was again admitted in March 1977.

On admission allopurinol was discontinued. He was feverish and looked ill and experienced moderate right upper quadrant abdominal distress. He was not jaundiced. His blood pressure was 130/85 mm Hg and pulse rate 84 beats per minute. The liver and spleen were not palpable.

Laboratory investigations showed: haemoglobin 15·3 g/dl; WBC $8{\cdot}9 \times 10^9$/l with 7% eosinophils; ESR 80 mm in first hour; normal urinary values; serum SGOT 60 IU; alanine transaminase 53 IU (normal 0-35 IU); alkaline phosphatase 31 KA units; total bilirubin 24 μmol/l (1·4 mg/100 ml) (normal 1·7-24 μmol/l (0·1-1·4 mg/100 ml)); total plasma protein 68 g/l (normal 55-88 g/l); serum albumin 25 g/l (normal 32-51 g/l); prothrombin and partial thromboplastin normal, and serum urate 0·9 mmol/l (5·5 mg/100 ml) (normal 0·33-1·3 mmol/l (2-7·6 mg/100 ml)). VDRL was nonreactive. No LE cells were seen. Blood cultures, tuberculin skin test, cryoglobulins, cytomegaloviral titres, Widal agglutination, and Paul-Bunnell tests were negative. Radiological examination included a normal chest radiograph. An oral cholecystogram and intravenous cholangiogram failed to opacify the gall bladder or biliary tree. A technetium scan showed diffuse patchy areas of decreased isotope uptake in the liver.

Laparotomy and cholecystectomy were performed. No calculi were found in the gall bladder, and an intraoperative cystic duct cholangiogram was negative for stones. A wedge biopsy of the liver showed multiple non-caseating granulomas, characterised by multinucleated giant cells (containing up to 50 nuclei), most of which were surrounded by epithelioid cells and a non-specific mononuclear cell infiltrate (see figure). The granulomas showed no particular acinar distribution. Many granulomas were in portal tracts as well as being distributed throughout the three zones of Rappaport's acinus.[5] Eosinophils were easily shown in the portal tracts containing granulomas. A mild degree of large droplet fatty change was evident, but there were no areas of focal necrosis. Glycogenated nuclei were present. Hepatocytes adjacent to and remote from the granulomas appeared normal. Special stains for acid-fast bacteria and fungi failed to show the presence of micro-organisms.

The patient's postoperative course was uneventful. On discharge, 16 days after allopurinol had been discontinued, his liver function values had returned to normal and the eosinophilia disappeared. He was discharged from hospital and advised to discontinue allopurinol. The patient remained well and returned six months later for an elective percutaneous liver biopsy. A 2·1-cm specimen, containing nine portal triads, did not show granulomas or inflammatory infiltrate in portal areas. Mild fatty change and glycogenated nuclei that had been shown on the previous biopsy persisted. Laboratory investigations were normal. The ESR was 5 mm in first hour, and the blood smear showed 2% eosinophils. Ten months after discontinuation of allopurinol the patient remained well.



Wedge biopsy of liver containing granulomas characterised by giant cells containing up to 50 nuclei. Liver adjacent to the granulomas is essentially normal. (H and E ×50.) Inset shows higher magnification of giant cells. Note epithelioid component of granuloma (arrowed). (H and E ×200.)

Comment

Hepatic granulomatosis is a non-specific pathological reaction to a wide variety of causal agents, the commonest being tuberculosis and sarcoidosis.[6] There are, however, a few reports of idiosyncratic adverse drug reactions resulting in hepatic granulomas.[4 7 8]

The liver is highly susceptible to predictable and unpredictable adverse drug effects. Unpredictable adverse drug reactions seem to occur in certain vulnerable individuals, leading to hepatic injury by either an allergic or an abnormal drug metabolic mechanism.[9] An abnormality in drug biotransformation that allows hepatotoxic concentrations of the drug or metabolite(s), or both, to accumulate may be a cause of drug-related liver damage in the idiosyncratic host.[9] These reactions are characterised by clinical symptoms after a variable latent period (weeks to months) with no accompanying fever, rash, eosinophilia, or granulomatous inflammation, and failure to reproduce hepatic injury with the challenge dose of the offending drug. The clinical and laboratory findings in our patient were clearly incompatible with the characteristics of this mechanism of adverse drug reaction. Similarly, the possibility that the liver reactions were secondary to deposition of hypoxanthine, xanthine, or oxypurine seems unlikely since no such crystalline material was seen.

Since hepatic adverse effects of allopurinol are rare, such reactions in susceptible hosts are probably immunologically mediated. In our patient physical examination, skin testing, and microbiological, biochemical, and radiological investigations did not identify a cause for the granulomas other than the drug. Furthermore, the patient showed signs and symptoms consistent with an allergic phenomenon. His symptoms of allergy (fever, malaise, eosinophilia, and granulomas) became clinically manifest six years after allopurinol was prescribed. Although a fixed sensitisation period of one to four weeks is characteristic of an allergic drug reaction,[9] hypersensitive cutaneous and

haematological reactions to allopurinol have been reported after months or years of medication.[1] Granulomatous reactions are also a known hypersensitivity response to insoluble antigen and may occur without any other associated signs of allergy.[10] Furthermore, this case provides direct evidence for an allopurinol-associated granulomatous reaction: after being re-exposed to the drug the patient showed a prompt exacerbation of his previous symptoms and abnormal liver function values. The reappearance of a dose-independent drug reaction when medication is resumed after a drug-free interval is consistent with a "definitive" adverse allergic reaction to that drug.[9 11]

Unfortunately, no serological evidence to prove an allergic mechanism is available. Circulating drug antibodies empirically associated with hepatic injury have not been shown. Furthermore, the significance of anti-liver and antimitochondrial antibodies in patients with drug-induced liver disease is uncertain and their relevance to an allergic mechanism is unclear. Serological study of our patient's serum was not undertaken.

The initial histological examination of the patient's liver biopsy specimen in March 1977 showed many granulomas in portal tracts and in all zones of the liver acinus. When the drug was permanently discontinued the clinical and biochemical abnormalities resolved within three weeks. The patient felt better, and when examined six months later had normal laboratory values and no granulomas in the liver. The granulomas probably disappeared much sooner, as suggested in cases of granulomatous hepatitis associated with sulphadimethoxine,[7] phenylbutazone,[8] and allopurinol.[4]

It is possible that we obtained an unrepresentative section of liver on needle biopsy, thereby missing an area of granuloma. But the sample contained nine portal tracts, and, compared with the diffuse distribution of the granulomas in the wedge biopsy, it is extremely unlikely that a sampling error could have accounted for the absence of granulomas.

It is not surprising that serum transaminase and alkaline phosphatase concentrations were mildly raised and that the bilirubin concentration was normal, even in the presence of numerous granulomas, as liver parenchyma adjacent to and remote from these areas appeared normal. The absence of histopathological evidence of hepatitis may also have accounted for the latent period (three weeks) between readministration of the drug and onset of symptoms.

The absence of respiratory symptoms and lymphocytosis and the presence of granulomas characterised by multinucleated giant cells and eosinophils differentiates our case from that reported by Eliakim *et al*,[12] who described a granulomatous hepatitis accompanying a self-limited febrile disease. Our case resembles in part that reported by Simmons *et al*.[4] Their patient developed an acute granulomatous hepatitis after one month's treatment with allopurinol which resolved two weeks after the drug was discontinued. In our patient, however, symptoms of an adverse drug reaction became apparent after six years of allopurinol medication and improved over three weeks. Direct evidence for an allergic drug reaction was also available, since our patient was inadvertently rechallenged with allopurinol, which resulted in a recurrence of fever, malaise, and gastrointestinal distress. Unlike the case reported by Simmons *et al*,[4] the granulomas were not associated with hepatitis.

In view of the increasing number of reports of granulomas associated with drug treatment, the clinician should take a careful drug history in such patients and consider drug reaction in the differential diagnosis after excluding infectious and multisystem diseases. Although the evidence is not conclusive, a causal association seems to exist between allopurinol and hepatic granulomas.

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[1] Woodbury, D M, and Fingle, E, in *Pharmacological Basis of Therapeutics*, ed L Goodman and A Gilman. New York and London, Macmillan, 1975.
[2] Butler, R C, *et al*, *Journal of the American Medical Association*, 1973, **237**, 473.
[3] Mills, R M, jun, *Journal of the American Medical Association*, 1973, **216**, 799.
[4] Simmons, F, Feldman, B, and Gerety, D, *Gastroenterology*, 1972, **62**, 101.
[5] Rappaport, A M, *Microvascular Research*, 1973, **6**, 212.
[6] Guckian, J C, and Perry, J E, *Annals of Internal Medicine*, 1966, **65**, 1081.
[7] Esperitu, C R, Kim, T S, and Levine, R A, *Journal of the American Medical Association*, 1967, **202**, 985.
[8] Goldstein, G, *Annals of Internal Medicine*, 1963, **59**, 97.
[9] Zimmerman, H J, in *International Encyclopaedia of Pharmacology and Therapeutics*, ed M Samter, Section 75, p 299. New York, Pergamon Press, 1972.
[10] Sell, S, in *Pathology*, ed W Anderson and J Kissane. St Louis, Mo, C V Mosby, 1972.
[11] Karsh, F E, and Lasagna, L, *Journal of the American Medical Association*, 1975, **234**, 1236.
[12] Eliakim, M, *et al*, *Lancet*, 1968, **1**, 1348.

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Prevalence of latent perhexiline neuropathy

Since the introduction of perhexiline therapy in angina pectoris, clinical evidence of toxic polyneuropathy has been reported for about one case per 1000 treated patients. Ganglioside storage[1] and cytoplasmic inclusion[2] in the Schwann cells have been described in such cases. Slowing of both sensory and motor conduction velocities (SCV and MCV) of various peripheral nerves has been observed in all reported cases.[3]

We performed an investigation to discover the prevalence of latent neuropathy in patients on perhexiline and to determine how useful various electrophysiological procedures were for detecting subclinical nerve disease.

Patients, methods, and results

Thirty-five patients who were receiving perhexiline were studied: none had clinical evidence of neuropathy or any other disease affecting the nerves. Three electrophysiological values were recorded: (*a*) cutaneous SCV of ulnar nerve, (*b*) MCV of ulnar and popliteal nerves, and (*c*) the H reflex of the soleus muscle. The results were compared with those of a control group of normal subjects of corresponding ages (group 2). All recordings were performed at the same temperature, with current electromyographical techniques.

Mean electrophysiological values (±SD) in patients (group 1) and controls (group 2). Percentages of patients with abnormal values (control mean ± 2 SD) are also shown

	Group 1 (n = 36)	% of patients with abnormal values	Group 2 (n = 15)	P value
Tibial nerve (soleus H reflex):				
Latency response (ms) ..	5·6 ± 1·0		5·0 ± 0·5	NS
Latency of H reflex (ms) ..	33·1 ± 3·4	37	30·5 ± 0·4	0·01
H max:M max amplitude ratio (%)	22·4 ± 15·9	65	45·2 ± 11·7	0·001
Ulnar nerve:				
Cutaneous sensory fibres CV (m/s)	50·4 ± 6·1		51·5 ± 3·9	NS
Motor fibres distal latency (ms)	3·4 ± 0·6	24	3·1 ± 0·3	0·05
Motor fibres, forearm CV (m/s)	53·9 ± 6·7		52·2 ± 5·7	NS
Popliteal nerve:				
Motor fibres distal latency (ms)	5·3 ± 0·8	30	4·8 ± 0·7	0·05
Motor fibres, leg CV (m/s) ..	49·6 ± 8·1		48·5 ± 4·1	NS

The results are shown in the table. The H reflex was disturbed in patients in group 1: 65% had a decrease of H max:M max amplitude ratio and 37% an increase in latency of the H reflex. Distal motor latencies were increased in both ulnar (24%) and popliteal (30%) nerves. No abnormality was found in the cutaneous SCV of ulnar nerve. No correlation between electrophysiological findings and the dose of perhexiline or length of treatment was observed.