Hepatotoxicity associated with use of D-penicillamine in rheumatoid arthritis

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SUMMARY Two patients with rheumatoid arthritis developed evidence of hepatotoxicity while receiving D-penicillamine. Both recovered after withdrawal of the drug. These cases and a review of the literature suggested that hepatotoxicity, though rare, should be added to the list of adverse reactions to D-penicillamine.

D-penicillamine has been used for the treatment of rheumatoid arthritis for over 10 years. The United Kingdom Multicentre Trial Group (1973) and several recent reports by Jaffe (1978) and others have added impetus to its use. It is the drug of choice for the treatment of patients with Wilson's disease or cystinuria and is also used in chronic aggressive hepatitis, scleroderma, macroglobulinaemia, and heavy metal toxicity. Several untoward reactions have been reported and are almost always reversible with discontinuation of the drug. This report describes hepatotoxicity, an uncommon complication in 2 patients treated with D-penicillamine for rheumatoid arthritis.

Case 1

A 43-year-old Caucasian woman developed sero-positive rheumatoid arthritis at age 32 one month after a normal delivery. Polyarthritis began in the fingers and knees and soon involved the neck, shoulders, and elbows. She had an excellent response to intramuscular gold, sodium thiomalate, and tolerated it without difficulty until it was discontinued in 1970 because she again became pregnant. From 1970 to 1975 she was in clinical remission and received no therapy.

In November 1975 polyarthritis and morning stiffness recurred, with no relief from up to 4·8 g of aspirin daily. Gold was reinstituted but had to be discontinued without benefit after the development of a rash. Aspirin 4·2 g per day, was continued. D-penicillamine, 250 mg daily, was initiated on 13 May, 1977. There was no history of cholelithiasis, penicillin allergy, or hepatitis. Complete blood count, platelet count, liver function tests and urine analysis were within normal limits.

Two months later routine physical examination was unchanged. Neither fever, icterus, nor hepatomegaly was noted. There was no known exposure to hepatitis. Laboratory evaluation at that time showed a lactic dehydrogenase (LDH) concentration of 405 units (normal 140–270 units), serum glutamic oxaloacetic transaminase (SGOT) of 440 units (normal 9–22 units), an alkaline phosphatase of 70 Bodansky units (normal 12–40 Bodansky units), a normal complete blood count (CBC), platelet count, creatine phosphokinase, urine analysis, and bilirubin. A test for hepatitis-associated antigen was negative.

D-penicillamine was stopped while aspirin was continued. The SGOT level gradually fell to 46 by 29 July, 1977, and on 23 September, 1977 it was 32. Therapy with D-penicillamine was then reinstituted; during the next 2 weeks the SGOT increased to 91 units. CBC was normal with 2% eosinophils. D-penicillamine was again discontinued, and by 6 December, 1977 the SGOT was 13 units. Active polyarthritis persists with a rheumatoid factor titre of 1:5120.

Case 2

A 60-year-old man presented with rheumatoid
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by fever, pruritus, rash, nausea, and slight eosinophilia. Penicillamine was discontinued. The rash and jaundice disappeared, and the laboratory findings became normal 1-2 weeks later. The authors concluded that a drug-induced hepatitis of the cholestatic type had been caused by D-penicillamine. Cholestatic jaundice developed also in a patient with rheumatoid arthritis 4 weeks after penicillamine was added to his regimen of salicylates and corticosteroids. He died in acute renal failure (Barzilai et al., 1978). Hepatocellular damage occurred in a 13-year-old girl with rheumatoid arthritis after combination therapy of D-penicillamine and benorylate (an ester of acetylsalicylic acid and acetaminophen) (Sacher and Thaler, 1977).

Hepatic damage caused by salicylates has been reported (Garber et al., 1975), but the first patient's continuing salicylate therapy and rising SGOT after D-penicillamine rechallenge argue against salicylate hepatotoxicity as the sole factor in her enzyme changes. To our knowledge there is no known association of tolmetin and hepatotoxicity. The only hepatic damage attributed to corticosteroids is fatty infiltration (Klatskin, 1969).

The suspected mechanisms of D-penicillamine toxicity include hypersensitivity; inhibition of pyridoxine metabolism especially by the L-isomer, which may contaminate the product; immune complex deposition seen in nephropathy (Jaffe, 1968; Lachmann, 1968); and possible localised areas of copper deficiency, with subsequent interference with collagen and elastin formation. D-penicillamine must also be considered a potent inducer of autoantibodies and autoimmune disease.

We are uncertain if these cases represent liver damage in the framework of a direct toxic or an idiosyncratic drug reaction. The possibility of hepatotoxicity in patients treated with D-penicillamine should be considered.

References


