Penicillamine in the treatment of rheumatoid arthritis

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Penicillamine, a compound which has found uses in widely different diseases, has recently shown promising results in rheumatoid arthritis (Jaffe, 1970; Golding, Wilson, and Day, 1970). We have used the drug in a small group of patients who had failed to respond to conventional therapy with a view to assessing its effectiveness and to learning more about its side-effects. We report our preliminary results, emphasizing that they are uncontrolled and that statements of effectiveness are therefore of limited value.

Methods

In all cases a slowly increasing dosage of penicillamine hydrochloride was used, starting with 300 mg./day and rising each week by 300 mg./day up to a total of 1,800 mg. daily. Progress was assessed using the articular index of Ritchie, Boyle, McInnes, Jasani, Dalakos, Grieson, and Buchanan (1968), measurement of joint size (Boardman and Hart, 1967), erythrocyte sedimentation rate and sheep cell agglutination titre. Renal function tests were carried out in all patients before the start of therapy and the urine was checked weekly for the presence of protein. Serum and 24-hr urinary iron and copper levels were measured in three patients.

Case reports

Three patients with rheumatoid arthritis and arteritis were treated with penicillamine because of the development of gangrene of the fingers and toes. In two of these cases there was no noticeable alteration in the course of the disease by penicillamine; in the third treatment was discontinued because of side-effects.

Case 1, a 55-year-old woman, with severe rheumatoid arthritis of 13 years' duration developed gangrene, first of the right great toe and then of the left foot, requiring amputation. She was started on penicillamine which produced a fall in erythrocyte sedimentation rate and Waaler-Rose titre; the only apparent clinical effect was that she became cushingoid and clearly required less steroid. After 4 months on penicillamine she developed mesenteric and myocardial infarctions and died.

At autopsy there were rheumatoid granulomata in the region of the aortic valve, from which coronary and mesenteric embolism had occurred.

Case 2, a 64-year-old woman, with rheumatoid arthritis of malignant type, developed gangrene of the left fifth toe, after only 3 years of disease. At this time she also had peripheral neuropathy, episcleritis, and aortic incompetence. She was treated with penicillamine with no obvious effect; after 3 months on the drug she developed gangrene of the left foot; after 5 months she became cachectic, developed congestive cardiac failure, and died.

At autopsy there were extensive rheumatoid granulomata throughout the myocardium and heart valves. Penicillamine was stopped 1 week before death because of persistent vomiting.

Case 3, a 70-year-old woman, with rheumatoid arthritis and gangrene of one finger, stopped penicillamine after 3 months because of persistent vomiting; there had been no obvious clinical change.

RESULTS IN PATIENTS WITH ACTIVE ARTHRITIS
Seven patients with active arthritis were given penicillamine because they had failed to respond to conventional therapy, including gold and periods of rest in hospital. There was a striking reduction in the number of tender joints, as shown by the articular index (Fig. 1).

FIG. 1 Articular index in seven patients receiving penicillamine

Changes in joint size and erythrocyte sedimentation rate are shown in Table I; the sheep cell agglutination titre fell by a mean of two dilutions at 3 months, and by 3.5 dilutions after 6 months of therapy. Two of these patients had vasculitic skin lesions which disappeared within 3 months of therapy. Urinary excretion of copper rose as expected but there was no change in urinary excretion of iron or in serum levels of either element.

Table I Changes in joint size (negative results indicating reduction) and erythrocyte sedimentation rate.

Means of seven cases

Time (mths)	Joint size (mm. change)	Erythrocyte sedimentation rate (mm./hr)
0	0	43.9
1	-1.6	40.9
3	-15.3	31.9
6	-13.1	24.1
9	-14.6	23.7

SIDE-EFFECTS

These are shown in Table II with the time (in months after starting penicillamine) at which they occurred.

Table II Side-effects of penicillamine, showing the time (in months after starting therapy) at which they occurred

Case no.	Nausea and vomiting	Loss of taste	Proteinuria	Rash
1				
2	5	2		
3	3			
4		1		
5			9	1
6			9	
7			7	
8			9	
9	3	3		
10	3	2		

There were four cases of nausea and vomiting, in three of which the drug was stopped with relief of symptoms. In one case it was possible to continue therapy at a lower dose. Four patients lost their taste but by this time they had improved and were

happy to trade taste for lack of arthritis; none stopped treatment for this reason and taste returned within 3 months while they were still on penicillamine therapy. Four patients developed proteinuria and treatment was stopped in all; two renal biopsies were carried out in patients with slight proteinuria (2 to 3 g. daily), one of which showed changes of immune complex nephritis; the other was normal by light and electron microscopy and on immunofluorescent staining. None of the patients with proteinuria showed any other abnormality of renal function and in all cases the proteinuria gradually lessened and disappeared, in one case after a year (Fig. 2). No patient became oedematous. In one case a rash appeared; treatment was stopped and restarted at a low dose without recurrence.

FIG. 2 24-hour urinary protein excretion in a patient who developed penicillamine nephropathy; the drug was stopped when proteinuria was detected

Discussion

Even though side-effects eventually demanded stopping treatment, the suppression of disease activity produced by penicillamine brought useful benefits in a number of cases. Five of the seven cases with active disease were able to return to work; in three steroid dosage was reduced; one man was able to undergo hip replacement which had been previously contraindicated by his generalized active disease. In one patient who has now been on penicillamine for 3 years, there was complete disappearance of rheumatoid nodules, splenomegaly, and peripheral neuropathy. These anecdotal experiences encourage us to proceed to controlled studies of the drug.

Our results in patients with gangrene were disappointing and not in accord with those of Jaffe (1970). A multicentre trial is urgently required to determine the value of penicillamine in this group of rare and often fatal cases.

Side-effects of penicillamine, though common and unpleasant, had the merit of being easily detected and completely reversible.

Summary

Penicillamine suppressed disease activity in seven patients with severe rheumatoid arthritis, but had no

effect in three with gangrene of the fingers or toes. Loss of taste, nausea, vomiting, and proteinuria were frequent but reversible complications.

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