Trial comparing D-penicillamine and gold in rheumatoid arthritis

Preliminary report*

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The Multicentre Trial Group (1973) showed that penicillamine was superior to placebo in a double-blind trial against placebo. In this trial penicillamine was compared with gold.

There are three reasons why a double-blind trial of penicillamine and gold was not attempted; first, gold is given by injection and penicillamine orally; secondly, both drugs have distinctive side effects which might 'unblind' the observer; and thirdly, because some side effects are potentially dangerous, it is essential that the physician knows which drug his patient is receiving. For these reasons, the patients were treated by their usual physicians who supervised dosage and documented side effects. Before the trial and at 3-monthly intervals after the start of treatment, the patients were seen by a 'blind' observer from another hospital.

Methods

Eighty-nine patients from three centres were admitted to the trial. All had definite or classical rheumatoid arthritis by the A.R.A. criteria (Committee of the American Rheumatism Association, 1959) of at least 6 months' duration, with an articular index (Ritchie, Boyle, McInnes, Jasani, Dalakos, Grieveson, and Buchanan, 1968) of at least eight, and an ESR of at least twenty-five. All were outpatients.

Patients were allocated to treatment with either gold or penicillamine according to a randomized schedule stratified for age, sex, steroid therapy, and type of anti-inflammatory drug therapy. As far as possible, patients were given aspirin alone; when this was not possible, they were given one other drug only; phenylbutazone was not permitted and patients who had received either gold or penicillamine in the past were excluded.

Gold was given in the form of sodium aurothiomalate (Myocrisin) in a dose of 10, 20, 30, and 40 mg weekly for the first 4 weeks, then 50 mg weekly up to a total dose of 1g, then 50 mg monthly. Penicillamine was given in an initial dose of 250 mg daily of base or 300 mg, daily of hydrochloride, increasing by 250 mg or 300 mg, respectively, every fortnight up to a total dose between 1 and 1.8 g daily according to response.

The following measurements were made before the start of treatment and at 3-monthly intervals thereafter: pain using a visual analogue scale; duration of morning stiffness; an assessment of progress (worse, unchanged, slightly, moderately, and much better); joint size (Boardman and Hart, 1967); grip strength; articular index (Ritchie and others, 1968); nodule count; ESR; latex test; sheep cell agglutination test.

Clinical measurements were made by two observers and all measurements of a particular patient were made by the same observer. The observer did not know which treatment the patient was receiving and patients were asked not to discuss their treatment or their side effects with the observer.

The results were analysed by Student's t-test; this was applied to differences between measurements at the start of the trial and after 3 and 6 months of treatment. Differences within treatment groups were analysed by Student's t-test applied to paired data. Correlation coefficients were used to examine relationships between different measurements and their significance tested by Student's t-test.

Results

Eighty-six patients completed at least 3 months' treatment. Three who were withdrawn in the first 3 months of the trial have not been included in the following analysis because no assessments were carried out; two were withdrawn for reasons unrelated to treatment, and one was unable to tolerate even one tablet of penicillamine.

Table I shows that the forty patients receiving gold and forty-six receiving penicillamine were well matched for sex, age, and duration of rheumatoid...
There are no significant differences between the groups.

Table I Characteristics of patients receiving either gold or penicillamine

<table>
<thead>
<tr>
<th></th>
<th>Gold</th>
<th>Penicillamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>Male: female</td>
<td>12:28</td>
<td>17:29</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>51.9</td>
<td>52.4</td>
</tr>
<tr>
<td>Duration of disease (yrs)</td>
<td>6.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Tables II and III show the changes in various measurements made after 3 and 6 months' treatment. All have been analysed using Student's t-test applied to differences between measurements at 3 or 6 months and those made before the start of the trial. In no case was a significant difference found between the effects of the two drugs.

Table II Mean initial levels and changes in clinical measurements after 3 and 6 months' treatment with penicillamine (P) or gold (G)

<table>
<thead>
<tr>
<th>Months of treatment</th>
<th>Pain</th>
<th>Duration of morning stiffness</th>
<th>Articular index</th>
<th>Grip strength</th>
<th>Joint size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G</td>
<td>P</td>
<td>G</td>
<td>P</td>
<td>G</td>
</tr>
<tr>
<td>0</td>
<td>14-2</td>
<td>14-1</td>
<td>104-5</td>
<td>99-6</td>
<td>23-6</td>
</tr>
<tr>
<td>3</td>
<td>+6-3</td>
<td>+6-2</td>
<td>+52-8</td>
<td>+48-8</td>
<td>+10-4</td>
</tr>
<tr>
<td>6</td>
<td>+6-3</td>
<td>+7-7</td>
<td>+59-9</td>
<td>+60-6</td>
<td>+11-8</td>
</tr>
</tbody>
</table>

* Figures indicate improvement.

Table III Mean initial levels and changes in laboratory measurements after 3 and 6 months' treatment with penicillamine or gold

<table>
<thead>
<tr>
<th>Months of treatment</th>
<th>ESR</th>
<th>Latex*</th>
<th>SCAT†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G</td>
<td>P</td>
<td>G</td>
</tr>
<tr>
<td>0</td>
<td>52-2</td>
<td>52-9</td>
<td>4-0</td>
</tr>
<tr>
<td>3</td>
<td>+15-7</td>
<td>+21-5</td>
<td>+1-2</td>
</tr>
<tr>
<td>6</td>
<td>+28-7</td>
<td>+23-7</td>
<td>+1-5</td>
</tr>
</tbody>
</table>

* Titres were scored: 1 = <1/20; 2 = 1/20; 3 = 1/40, etc.
† 1 = <1/16; 2 = 1/16; 3 = 1/32, etc.
+ Figures indicate improvement.
penicillamine. Rashes or pruritus accounted for twelve of the fourteen gold withdrawals. Two patients receiving gold and two receiving penicillamine were withdrawn because of heavy proteinuria or nephrotic syndrome. One patient receiving penicillamine was withdrawn because of nausea and vomiting. Four patients were withdrawn for reasons unrelated to treatment.

Fig. 2 shows the incidence of clinically important side effects and it is clear that there is a large excess of these attributable to penicillamine in the first 2 months of treatment. Of these side effects, rashes (Fig. 3) occurred in 32.5% of patients receiving gold and in 24% of those receiving penicillamine. The penicillamine rashes occurred earlier and in no case caused withdrawal of treatment for more than a week or two. All but one of the patients receiving gold who developed rashes were withdrawn; gold therapy was restarted in this patient, but the rash recurred after 3 months. Apart from rashes and two cases of heavy proteinuria, no other important side effects were noted in patients receiving gold.

Fig. 4 shows the incidence of some other side effects of penicillamine. Loss of taste occurred in 24% of patients during the first 3 months of the trial, lasted 4–8 weeks, and did not necessitate withdrawal of treatment. Gastrointestinal disturbances occurred in 33% of patients, also commonly in the first 3 months of treatment, with nausea and anorexia being the commonest symptoms. 27% of these episodes were associated with loss of taste. In the 4th, 5th, and 6th months, six patients (13%) developed thrombocytopenia with levels between 46,000 and 110,000 platelets/mm³; in one case this was associated with haemoptysis and in another with haematuria. In all cases, the platelet count returned rapidly to normal with prompt withdrawal of penicillamine and treatment was later restarted at a lower dose. Transient slight proteinuria was common in patients receiving...
Discussion

On present evidence, there is little to choose between penicillamine and gold therapy in the management of patients with active rheumatoid disease which has failed to respond to simpler measures; in the first 6 months of treatment, gold and penicillamine were equally effective. Gold treatment had to be withdrawn much more frequently than penicillamine because of rashes which occurred in about one third of cases. However, there were more side effects on penicillamine, particularly loss of taste, rashes, gastrointestinal disturbance, and thrombocytopenia; these were usually transient and did not prevent the continuation of treatment. The incidence of heavy proteinuria was equal in the two groups, but since penicillamine nephropathy is commonly encountered after 9 months of treatment, more cases may be expected in the next 6 months of the trial.

Summary

In the first 6 months of a comparative study in patients with rheumatoid arthritis, penicillamine and gold were equally effective. Penicillamine caused more side effects but the side effects which occurred in patients receiving gold were more likely to require withdrawal of treatment.

References


Multicentre Trial Group (1973) Lancet, 1, 275 (Controlled trial of D-penicillamine in severe rheumatoid arthritis)

Trial comparing D-penicillamine and gold in rheumatoid arthritis. Preliminary report.
E C Huskisson, T J Gibson, H W Balme, H Berry, H C Burry, R Grahame, F D Hart, D R Henderson and J A Wojtulewski

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