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# Maintenance dose of penicillamine in rheumatoid arthritis: a comparison between a standard and a response-related flexible regimen

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SUMMARY There is much individual variation in the response of rheumatoid arthritis (RA) to penicillamine, some patients deriving benefit from very small doses. A dose of 750 mg daily is widely regarded as standard, and, while their RA commonly responds, many patients discontinue treatment because of adverse reactions to penicillamine. A more flexible prescribing policy might be more successful in the long term and was tested in 1 group of 20 patients, another receiving a 'standard' regimen, each beginning treatment at a low dose level. Of those who were given increases of dose only if response was poor 17 completed 1 year of treatment on an average maintenance dose of 308 mg daily, but only 11 of the other group on an average dose 613 mg daily. Proteinuria, which was found only in the latter group accounted for 6 withdrawals, all at doses of 625 mg daily or above. The reduction in rheumatoid activity appeared to be of about the same degree among the members of both groups who completed 12 months of treatment. Penicillamine should be given initially in a low dose and this should be raised only if there is lack of response after at least 4 weeks.

Penicillamine in a total daily dose of 1·5 g benefits most patients with rheumatoid arthritis who are able to tolerate this amount (Multicentre Trial Group, 1973). Many cannot, so that it is now customary to prescribe no more than 750 mg daily (Hill, 1977). Furthermore, maintenance doses as low as 125 mg daily have been shown often to be effective (Day *et al.*, 1974). To prevent a high incidence of adverse reaction early in treatment gradual introduction of the drug has long been standard practice (Jaffe, 1968), and since there is great individual variation in response there may be a case for increasing doses only if indicated rather than to follow a predetermined regimen.

One of our 2 clinics has for some time adopted a 'response' related (R) and the other a 'standard' (S) regimen, aiming at a maintenance dose of 750 mg. Having taken part together in an earlier study of penicillamine (Multicentre Trial Group, 1973) we have compared our respective regimens in a formal trial with the aim of determining which method of prescribing is in practice the more successful.

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## Patients and methods

Twenty consecutive patients attending clinics at St James's Hospital, Leeds, or the Royal Bath Hospital, Harrogate, were admitted to the trial of the flexible (R) regimen and 20 attending at Stoke Mandeville Hospital to the (S) regimen. The criteria for admission were: (*a*) definite or classical rheumatoid arthritis (ARA criteria); (*b*) failure of response to an adequate dose of at least 1 anti-inflammatory drug for at least 3 months.

Patients who had within the past three months received gold, immunosuppressive drugs, chloroquine, or a daily total of more than 7·5 mg of prednisolone (or its equivalent) were excluded, as were patients who had ever received penicillamine. Substitution for patients withdrawing within the trial course of 12 months was permitted only if such withdrawal had been for reasons other than lack of effect or adverse reaction to the drug.

### TREATMENT

Patients who entered the study while taking anti-inflammatory drugs, including small doses of prednisolone, continued to take them, but changes of

Table 1 *Summary of characteristics of 2 scores in tests at beginning (0) and end (12) of trial by 11 patients given 'standard' regimen*

| *Patient* | *Age (years)* | *Sex* | *Duration of RA (years)* | *Maintenance penicillamine (mg)* | *Pain (0–3)* | | *Stiffness (min)* | | *Tenosynovitis* | | *Painless joints (0–16)* | | *Disease activity (0–3)* | | *SCAT (tubes)* | | *ESR (mm/1 h)* | | *Maintenance prednisolone (mg)* | | *Use of NSAID** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 |
| 1 | 52 | F | 4 | 1000 | 2 | 2 | 120 | 120 | + | 0 | 0 | 6 | 3 | 1 | 9 | 0 | 72 | 46 | 5 | 5 | + | + |
| 2 | 52 | F | 6 | 750 | 1 | 2 | 60 | 30 | + | + | 8 | 4 | 3 | 2 | 6 | 6 | 100 | 40 | 0 | 0 | + | + |
| 3 | 36 | M | 7 | 500 | 2 | 2 | 0 | 0 | + | 0 | 8 | 14 | 2 | 1 | 9 | 7 | 102 | 10 | 5 | 5 | + | + |
| 4 | 67 | M | 18 | 500 | 2 | 1 | 60 | 0 | + | 0 | 10 | 13 | 2 | 1 | 6 | 0 | 93 | 56 | 5 | 5 | + | + |
| 5 | 45 | M | 21 | 750 | 2 | 1 | 120 | 120 | + | + | 13 | 16 | 1 | 1 | 0 | 0 | 6 | 9 | 0 | 0 | + | + |
| 6 | 57 | F | 8 | 500 | 2 | 0 | 60 | 0 | + | + | 4 | 14 | 2 | 1 | 7 | 0 | 88 | 35 | 0 | 0 | + | + |
| 7 | 51 | M | 16 | 500 | 0 | 1 | 2 | 0 | + | 0 | 9 | 15 | 1 | 1 | 9 | 7 | 39 | 12 | 5 | 5 | + | + |
| 8 | 60 | M | 0·66 | 500 | 3 | 0 | all day | 0 | 0 | 0 | — | 16 | 3 | 0 | 7 | 0 | 77 | 2 | 0 | 0 | + | 0 |
| 9 | 52 | F | 9 | 750 | 2 | 2 | — | 0 | 0 | 0 | 7 | 12 | 2 | 1 | 0 | 0 | 13 | 16 | 5 | 5 | 0 | 0 |
| 10 | 44 | F | 4 | 500 | 3 | 1 | 90 | 60 | + | 0 | 0 | 1 | 2 | 1 | 5 | 0 | 3 | 12 | 5 | 5 | + | + |
| 11 | 27 | F | 0·15 | 500 | 3 | 1 | 60 | 0 | + | 0 | 0 | 14 | 3 | 1 | 5 | 0 | 60 | 22 | 5 | 5 | + | 0 |

*NSAID = nonsteroidal anti-inflammatory drugs

Table 2 *Summary of characteristics of 2 scores in tests at beginning (0) and end (12) of trial by 17 patients given 'response related' regimen*

| Patient | Age (years) | Sex | Duration of RA (years) | Maintenance penicillamine (mg) | Pain (0–3) | | Stiffness (min) | | Tenosynovitis | | Painless joints (0–16) | | Disease activity (0–3) | | SCAT (tubes) | | ESR (mm/1 h) | | Maintenance prednisolone (mg) | | Use of NSAID | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 | 0 | 12 |
| 12 | 55 | M | 15 | 750 | 3 | 2 | 300 | 180 | 0 | 0 | 4 | 10 | 2 | 2 | 0 | 0 | 35 | 23 | 5 | 0 | 0 | 0 |
| 13 | 69 | F | 10 | 125 | 2 | 1 | all day | 30 | 0 | + | 6 | 11 | 3 | 1 | 0 | 0 | 5 | 3 | 0 | 0 | + | 0 |
| 14 | 65 | F | 8 | 250 | 1 | 0 | 60 | 0 | 0 | 0 | 13 | 16 | 1 | 0 | 5 | 4 | 34 | 1 | 0 | 0 | 0 | 0 |
| 15 | 58 | M | 19 | 875 | 1 | 2 | 0 | 30 | 0 | 0 | 8 | 9 | 2 | 2 | 4 | 0 | 98 | 29 | 7·5 | 7·5 | + | + |
| 16 | 56 | F | 8 | 375 | 2 | 0 | 30 | 10 | 0 | 0 | 11 | 15 | 1 | 1 | 4 | 0 | 85 | 39 | 0 | 0 | 0 | 0 |
| 17 | 69 | M | 11 | 250 | 2 | 0 | 5 | 0 | 0 | 0 | 11 | 16 | 3 | 0 | 0 | 0 | 32 | 5 | 0 | 0 | + | + |
| 18 | 32 | F | 7 | 250 | 1 | 0 | 0 | 0 | + | 0 | 15 | 16 | 1 | 0 | 5 | 0 | 54 | 23 | 0 | 0 | + | 0 |
| 19 | 69 | F | 10 | 250 | 2 | 1 | 60 | 0 | + | 0 | 8 | 13 | 2 | 1 | 5 | 2 | 60 | 29 | 0 | 0 | + | 0 |
| 20 | 49 | F | 6 | 250 | 2 | 0 | 60 | 20 | 0 | 0 | 15 | 14 | 1 | 0 | 6 | 5 | 72 | 90 | 0 | 0 | + | 0 |
| 21 | 51 | F | 6 | 250 | 2 | 2 | 30 | 10 | 0 | 0 | 6 | 12 | 2 | 2 | 0 | 0 | 53 | 20 | 0 | 0 | + | + |
| 22 | 57 | M | 12 | 250 | 1 | 1 | 60 | 0 | 0 | 0 | 10 | 13 | 3 | 1 | 0 | 0 | 40 | 30 | 0 | 0 | 0 | 0 |
| 23 | 68 | M | 11 | 250 | 2 | 3 | 90 | 90 | + | 0 | 7 | 9 | 2 | 1 | 7 | 4 | 47 | 10 | 0 | 0 | + | + |
| 24 | 69 | F | 13 | 375 | 3 | 1 | 30 | 15 | + | 0 | 7 | 13 | 3 | 1 | 3 | 2 | 31 | 18 | 0 | 0 | + | + |
| 25 | 38 | F | 10 | 250 | 2 | 1 | 60 | 30 | + | + | 14 | 14 | 3 | 1 | 6 | 0 | 23 | 20 | 0 | 0 | + | + |
| 26 | 53 | F | 7 | 250 | 2 | 1 | 30 | 20 | + | 0 | 9 | 13 | 2 | 1 | 6 | 5 | 40 | 16 | 0 | 0 | + | + |
| 27 | 56 | F | 7 | 125 | 1 | 1 | 180 | 20 | + | 0 | 12 | 13 | 2 | 1 | 5 | 2 | 89 | 47 | 0 | 0 | + | 0 |
| 28 | — | F | 9 | 125 | 1 | 1 | 10 | 10 | + | + | 9 | 14 | 2 | 1 | — | — | 38 | 13 | 0 | 0 | + | 0 |

dose or drug were recorded. The trial regimens were as follows.

*Response related.* (*R*) Initial dose 125 mg daily increased by 125 mg increments at not less than 4-week intervals to the maintenance dose judged to be producing an acceptable response.

*Standard* (*S*). 250 mg daily increasing by 250 mg at 4-week intervals to 750 mg. Further increases or reductions were permitted after 6 months of treatment.

MEASUREMENTS

The signs and symptoms were assessed as follows: (1) Pain over the last 2 days before examination categorised as nil (0), slight (1), moderate (2), or severe (3). (2) Morning stiffness recorded in minutes by the patient. (3) Number of joints with a full range of painless active movement at examination. In this test 16 joints or groups of joints were examined (right and left elbow, shoulder, hip, knee, ankle, with metacarpophalangeal, wrist, and metatarsophalangeal joints each being counted as one). The total was recorded out of the maximum of 16. (4) Presence or absence of tenosynovitis was used as an indication of extra-articular inflammation. (5) The observer's opinion of the degree of activity of the disease was recorded as remitted (0), slight (1), moderate (2), or severe (3). (6) Laboratory tests comprised measurements of erythrocyte sedimentation rate (ESR), H6, sheep cell agglutination titre, leucocyte and platelet counts, and examination for proteinuria.

FREQUENCY OF ASSESSMENT AND RECORDS

Full assessments were made initially and at 3, 6, 9, and 12 months, and findings were recorded on the standard form on which adverse effects and treatment were also entered. In addition, monthly 'safety' checks were made.

## Results

Of the 40 patients initially entering the trial 1 was replaced because of failure to attend shortly after starting treatment. The 2 equal sized groups were comparable with respect to age and duration of disease. Of those treated by the S regimen 11 were women and 13 men were taking 5 mg daily of prednisolone, as opposed to 13 and 3 respectively in the R group. In several respects the patients in the S group appeared to be the more severely affected, but the differences between the group means of the scores in individual tests did not using the Student *t* test, reach the conventional level of statistical significance of 5%.

Seventeen patients in the R and 11 in the S group completed 1 year of treatment. The initial and final scores in the various tests of these patients' progress are summarised in Tables 1 and 2. No patient in either group was considered to have more active disease at the end than at the beginning, and both groups had improved their scores in each test to a comparable and significant degree. The group mean scores at 12 months were again closely similar to each other. The numbers of patients within each group who had improved by 50% or more in their individual scores were also comparable (Table 3).

The higher doses of the S regimen did not produce a detectably more rapid improvement than those of the R regimen as judged by assessments at 3, 6, and 9 months. There was some reduction in the numbers needing anti-inflammatory drugs of the non-steroidal type, mainly in the R group, but little reduction in the use of prednisolone. Three patients in each group received a single intra-articular injection of hydrocortisone during the trial. The main difference in treatment between the groups was that the average daily maintenance dose of penicillamine in the S group (613 mg) was double that given to the R group (308 mg).

WITHDRAWALS FROM TREATMENT

Twelve patients were unable to complete the course (Table 4), 9 from the S and 3 from the R group. Six were lost from the S group because of proteinuria (2 of these also developing a rash) and 1 because of thrombocytopenia. Neither proteinuria nor thrombocytopenia caused losses from the R group. One succumbed to myocardial infarction at 12 months. There were no withdrawals because of lack of therapeutic benefit.

ADVERSE REACTIONS NOT LEADING TO WITHDRAWAL

Five of the 11 patients of the S group who completed the course experienced an adverse reaction. Three of these suffered impairment of taste, 2 of whom also experienced anorexia, which required a temporary reduction in dose. One patient had epigastric discomfort and another a pemiphigus-like reaction that responded to an 8-week interruption of treatment.

Table 3 *Numbers of patients (expressed as percentage of each treatment group) whose individual scores improved between 0 and 12 months by 50% or more*

| *Regimen* | *n* | *Pain* | *Duration of stiffness* | *Painless joints* | *ESR* | *SCAT* | *Disease activity* |
|---|---|---|---|---|---|---|---|
| S | 11 | 55 | 55 | 73 | 55 | 55 | 73 |
| R | 17 | 53 | 65 | 71 | 71 | 42 | 82 |

Table 4 *Causes of withdrawal before completion of 12 months in trial*

| *Regimen* | *Age* | *Sex* | *Dose of penicillamine at withdrawal (mg)* | *Cause* | *Duration of treatment up to withdrawal (months)* |
|---|---|---|---|---|---|
| S | 67 | F | 750 | Proteinuria 2·29 g/24 h | 10 |
| | 43 | F | 1000 | Proteinuria 0·9 g/24 h | 6 |
| | 56 | F | 750 | Proteinuria 6·8 g/24 h | 10 |
| | 50 | F | 625 | Proteinuria 4·7 g/24 h | 10 |
| | 67 | M | 750 | Proteinuria 2·2 g/24 h | 7 |
| | 63 | M | 750 | Proteinuria 4·2 g/24 h | 7 |
| | 46 | F | 750 | Urticaria | 3 |
| | 36 | M | 750 | Thrombocytopenia 11·0 × $10^9$/l | 2 |
| | 62 | M | 250 | Coronary thrombosis | 12 |
| R | 41 | M | 250 | Rash | 6 |
| | 71 | M | 125 | Peeling skin | 4 |
| | 56 | F | 250 | Confusion | 7 |

Four of the 17 survivors of the R group had adverse reactions—dyspepsia, thrombocytopenia, and rash each in 1 patient, all responding to a temporary reduction of dose. One patient complained of impaired taste. None of the patients of the R treatment group developed proteinuria.

## Discussion

It is clear that the more flexible R regimen was much the better tolerated, especially by the kidney. Side effects among the S group were twice as frequent and led to 3 times as many withdrawals as in the R group. There was no correlation between age or other drug treatment and withdrawal because of adverse reaction. Proteinuria occurred only in response to doses of 625 mg daily or above in this trial but like marrow depression may be precipitated by lower doses, so that the necessity for constant vigilance remains even when doses as low as 250 mg daily are not exceeded.

The R regimen permitted more patients to complete 12 months of treatment than did the S regimen, rendering any comparison of their therapeutic efficacy problematical, especially as the groups were not perfectly matched in respect of disease severity at the outset. Generally, however, both regimens benefited most patients who completed 12 months of treatment, and neither emerged as convincingly superior to the other in this respect. Jaffe (1977) found that patients taking 250 mg of penicillamine daily gained relief from their symptoms more slowly than those taking 1 g or more, although changes in the ESR and haemoglobin took place just as rapidly at both dose levels. Our patients treated by the S regimen appeared to respond no more quickly than those managed by the flexible schedule, possibly because the difference in dose between the 2 groups was not very large. Penicillamine is a suppressive drug in rheumatoid arthritis and to be useful must be taken indefinitely by most patients. We conclude that, unless a low dose is to be maintained throughout, prolonged treatment is likely to be most feasible if a response-related regimen is adopted.

The data collected in this study were subjected to statistical analysis by Dr A. Barr and Mrs Sheila Rogers, of the Oxford Regional Health Authority. We acknowledge their assistance and advice with gratitude.

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