Synthetic D(-)penicillamine in rheumatoid arthritis

Double-blind controlled study of a high and low dosage regimen

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Dixon, A. St. J., Davies, J., Dormandy, T. L., Hamilton, E. B. D., Holt, P. J. L., Mason, R. M., Thompson, M., Weber, J. C. P., and Zutshi, D. W. (1975). *Annals of the Rheumatic Diseases*, 34, 416-421. Synthetic D(-)penicillamine in rheumatoid arthritis. Double-blind controlled study of a high and low dosage regimen. Doses of both 600 mg and 1200 mg of D(-)penicillamine daily were superior to a standard regimen of therapy in rheumatoid arthritis. The higher dose did not produce significantly greater therapeutic benefit in the group of patients so treated, although individual patients sometimes improved more. The frequency of rashes, blood dyscrasias, and withdrawals from the trial increased with the dosage. It is concluded that D(-)penicillamine is a useful treatment, that the daily dose should be as low as possible, and that it should be increased at infrequent intervals only, with due regard to the likelihood of further improvement in relation to an increased risk of adverse reactions.

The precise mode of action of D(-)penicillamine in rheumatoid arthritis is still unknown although its ability to reduce the titre of rheumatoid factor is well established (Dresner and Trombly, 1960; Griffin, Ulloa, Henry, Johnston, and Holley, 1960; Jaffe, 1962, 1963). Its efficacy in the treatment of rheumatoid disease was indicated in Britain, first by a pilot study (Golding, Wilson, and Day, 1970) and subsequently by a 12-month double-blind study (Multicentre Trial Group, 1973). The original patients were reported (Day, Golding, Lee, and Butterworth, 1974) after treatment had extended in some instances for as long as 5 years. The authors concluded that smaller doses of penicillamine than are usually advocated are often effective and cause fewer adverse reactions.

Patients and methods

A double-blind controlled multicentre trial comparing the therapeutic effect and adverse effects of penicillamine in a

dosage of either 600 mg or 1200 mg daily in patients under fixed standard treatment is reported. A third group of patients acted as a control group, receiving the standard treatment and a minimal subeffective dose of penicillamine (12 mg daily).

The penicillamine base used was wholly synthetic*; it is prepared by a multistage synthesis from the appropriate amino acid precursor as opposed to semisynthetic penicillamine which is prepared by the acid hydrolysis of benzylpenicillin. The material contains 0.3% of the optical isomer, L(+)-penicillamine, which is regarded as toxic.

Outpatients at 5 hospital centres over the age of 16 years and having seropositive erosive disease classifiable as 'classical' or 'definite' (ARA, 1959) were studied. Informed consent was obtained from them after the purpose of the study was explained. Patients excluded from the study were pregnant women and women of child-bearing age not on stable contraceptive measures, patients with known penicillin allergy, those with pre-existing renal impairment, patients on zinc insulins, and those

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currently receiving treatment with gold, phenylbutazone, immunosuppressive agents, or a chloroquine derivative.

Patients were allocated to a 'general' group and a 'nodule' group, the latter group having well-defined rheumatoid nodules. Those in the general group were randomly allocated to a control subgroup (C) or to one of two treated subgroups (600 or 1200). Dosage was started with one tablet daily* and increased by one tablet fortnightly so a maximum dosage of four tablets daily was reached by the beginning of the seventh week. Treatment was maintained at this level where possible for the duration of the trial (24 weeks). Patients in group C received only control tablets containing 3 mg of penicillamine base. The daily dose for group 600 was supplemented with control tablets so it did not exceed 600 mg (actually 606 mg because of the small amount of penicillamine in the control tablets). The 1200 group received 1200 mg daily. Each patient, therefore, received an equal number of physically indistinguishable tablets at every stage of the trial. Patients in the nodule group were allocated to only two treatment subgroups, C and 1200, the same procedure being followed as for the general group.

CONCOMITANT TREATMENT

All patients were permitted a standard regimen of therapy which included analgesics containing aspirin or its derivatives, or paracetamol. Patients entering the trial on a stable dosage of indomethacin or corticosteroids were maintained on this treatment throughout.

CLINICAL MEASUREMENTS

The following measurements were done one week before the trial started (day -7) and at its start (day 0), and were repeated at 4-week intervals throughout the trial.

(1) The patient's subjective pain assessment graded from 0 (nil) to 4 (very severe). (2) Duration of morning stiffness of the joints in minutes. (3) Physical ability by the clinicians' assessment of the ARA Functional Class (Steinbrocker, Traeger, and Batterman, 1949)†. (4) Grip-strength (the mean of 3 readings in mmHg, using a mercury sphygmomanometer with an adapted bag initially inflated to 20 mmHg). (5) Haemoglobin concentration (g/dl).

X-rays of the hands and feet and the size and the number of rheumatoid nodules were compared at day 0 and at 24 weeks. Rose-Waaler, latex fixation, and antinuclear factor tests were done at day 0, 12, and 24 weeks. Serum copper and zinc estimations were made at day -7, day 0, and 12 and 24 weeks. Serum aspartate aminotransferase (SGOT), alkaline phosphatase, and serum bilirubin estimations were made at each attendance.

WITHDRAWAL CRITERIA

Withdrawal criteria included severe loss of taste, rashes, marked neutropenia or thrombocytopenia $<100000/\text{mm}^3$, persistent albuminuria >2 g daily, or any other apparent adverse reaction severe enough to justify withdrawal, including marked clinical deterioration of the arthritis.

Results

In the final assessment of the efficacy of penicillamine, results from the general group and the nodule group were combined. Table I shows the comparability of the three treatment subgroups at the start of the trial.

* 300 mg D(-)penicillamine base.

† The four grades I-IV given numerical values 1-4.

Table I Comparability of treatment subgroups

Parameter	C	600	1200
No. of patients at start			
Women	29	26	27
Men	14	8	17
Mean ages ($\pm$ SD) (yr)	53.5 $\pm$ 15.6	51.9 $\pm$ 3.7	54.8 $\pm$ 9.52
Mean duration ($\pm$ SD) of disease (yr)	9.8 $\pm$ 7.6	7.6 $\pm$ 6.2	8.6 $\pm$ 8.9
Mean grip-strength at day 0 (mmHg)			
R	123	131	133
L	118	129	125
Pain at day 0			
Gradings	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Frequency	2 4 19 13 5	0 1 14 16 2	2 4 18 10 7
Mean ESR at day 0 (mm/1st h)	49	53	51
Mean Hb ($\pm$ SD) at day 0 in patients completing trial (g/dl)	12.7 $\pm$ 1.2	12.5 $\pm$ 1.0	12.5 $\pm$ 1.5
No. of patients receiving concomitant corticosteroids	28	24	23

Distribution of the above factors was assessed by one-way analyses of variance, χ^2 tests, or t-tests, and confirmed to be randomly distributed ($P > 0.05$) in all cases.

CLINICAL ASSESSMENTS

All values at day -7 were compared with those at day 0 and absence of significant variation confirmed. Mean values for the control group and for the two treated groups at each of the six 4-week periods were then compared with the day 0 values and the differences analysed. For simplification of Tables II-V, only values at 4, 12, and 24 weeks are shown.

(1) Patients' pain assessment (Table II)

Wilcoxon's signed rank sum test was also used since this method of grading pain is nonparametric, and the results obtained were similar. In Table II, and in all other comparisons in this paper, NS is held to mean $P < 0.05$.

(2) Physical ability (physicians' grading on ARA scale)

These results were analysed in a similar way to those of the patients' pain assessment and although there was a greater reduction in grading, and hence increased physical ability in the 1200 group at 24 weeks compared with both of the other groups, the differences were not statistically significant either by analyses of variance or by the Wilcoxon test.

(3) Duration of morning stiffness

Analyses of variance showed no significant differences between any of the groups at either 4, 12, or 24 weeks. The Wilcoxon test gave the following results: C v. 600, $P < 0.05$ at 12 and 24 weeks; C v. 1200, $P < 0.05$ at 12 but not significant at 24 weeks; 600 v. 1200, not significant.

(4) Grip strength

Table III Mean differences from day 0 for each group (mmHg $\times$ 100 to remove decimal points)

Weeks	C		600		1200		Overall treatment effect	C v. treated groups		600 v. 1200	
	L	R	L	R	L	R		L	R	L	R
4	648	176	122	231	847	74	NS	NS	NS	NS	NS
12	1322	1165	2392	3352	3109	3100	NS	NS	$P < 0.05$	NS	NS
24	1409	514	3308	3771	4774	4185	$P < 0.05$	$P < 0.01$	$P < 0.01$	NS	NS

Analyses of variance. Figures indicate extent of improvement. L = left hand; R = right hand.

(5) ESR

Table IV Mean differences from day 0 for each group (mmHg $\times$ 100 to remove decimal points)

Weeks	C	600	1200	Overall treatment effect	C v. treated groups	600 v. 1200
4	423	21	-124	NS	NS	NS
12	-325	-2420	-1850	$P < 0.01$	$P < 0.001$	NS
24	-703	-2450	-2200	$P < 0.05$	$P < 0.01$	NS

Analyses of variance. Negative values indicate improvement.

Table II Group mean differences from day 0

Weeks	C	600	1200	Overall treatment effect	C v. treated groups	600 v. 1200
4	119	104	325	NS	NS	NS
12	50	958	656	$P < 0.001$	$P < 0.001$	NS
24	111	958	808	$P < 0.01$	$P < 0.001$	NS

Values have been multiplied by 10^3 to remove decimal points. Larger differences, and hence greater values, indicate greater pain relief. Analyses of variance.

(6) Haemoglobin

Table V Mean haemoglobin values (g/dl) (t-tests)

<i>Weeks</i>	<i>C</i>	<i>600</i>	<i>1200</i>	<i>Significance of increases from day 0</i>		
0	12.69	12.48	12.54	<i>C</i>	<i>600</i>	<i>1200</i>
12	12.66	12.62	13.06	—	NS	NS
24	12.66	13.25	13.46	—	P < 0.01	P < 0.05

EFFECT OF DISEASE DURATION ON CLINICAL RESPONSE

Arthritis in 34 patients was of 2 years' duration or less and that of 87 longer. The Wilcoxon signed rank sum test was used to analyse the six clinical assessments used previously and no consistent differences were

found between the two groups except in relation to subjective pain relief which was greater ($P < 0.01$) for the 'over 2-year' group at 12 and 24 weeks.

ASSESSMENT OF NUMBER OF PATIENTS IMPROVING IN EACH GROUP

The number of patients improving in each treatment group (as opposed to the extent of improvement described above) was evaluated 'blind' by one of us (J.C.P.W.) not directly concerned with assessing the patients. Patients were selected who showed between day 0 and week 24 either an obvious and consistent downward trend of two or more grades in pain rating, an upward trend of 20 mm or more in grip strength of either hand, or a consistent fall in ESR of 10 mm or more. Results of this analysis showed highly significant overall treatment effects ($P < 0.001$) for all the parameters examined, but at no time were the differences between the two treatment groups (600 and 1200) significant. For the sake of brevity only one parameter (grip-strength) will be examined here in detail. The values obtained for this are shown in Table VI.

Calculations were made in only those patients who completed the 24-week course of treatment in order to learn whether the higher dose of penicillamine had effected improvement in a greater number of patients who were still able to take it.

X-RAYS OF HANDS AND FEET

X-rays of hands and feet were taken where possible at day 0 and at 24 weeks, and were interchanged among the 5 different centres for reading and assessment of the number and severity of erosions and as to the observer's overall impression. Interobserver error and repeatability of grading had been ascertained as satisfactory in previous studies. Overall impression

Table VI Number of patients whose grip-strength improved

Class	C	600	1200
Improved	10 (26%)	14 (56%)	19 (70%)
Not improved	29	11	8
Totals	39	25	27

Table VII Data on adverse reactions

	C	600	1200	Overall significance
Total number of adverse reactions	21	25	48	
Ratio of adverse reactions to patients at risk	0.5	0.7	1.1	
No. of patients complaining	15 (34%)	17 (50%)	30 (67%)	$P < 0.02$ (χ^2 test)
No. of patients whose treatment was stopped due to adverse reactions	4 (9%)	9 (26%)	18 (40%)	$P < 0.01$ (χ^2 test)

was graded from +2 through 0 (no change) to -2. There was no evidence of any trend, either for better or worse, in any of the treatment groups.

EFFECT ON SIZE AND NUMBER OF RHEUMATOID NODULES

No significant changes were found either in the size or number of rheumatoid nodules assessed by soft tissue radiography.

IMMUNOLOGICAL AND BIOCHEMICAL TESTS

Quantitative Rose-Waaler tests were available on 19 patients in C group and on 15 and 11 patients, respectively, in the 600 and 1200 groups. Consideration of the standard error of the dilution factor indicated that a decrease in titre of two dilutions would be well outside the 95% confidence limits for the series. 16% of the control patients, 13% of the 600 group, and 45% of the 1200 group showed such a decrease at 24 weeks. This is compatible with the well-known ability of penicillamine to reduce rheumatoid factor, though, owing to the small numbers, these results are not statistically significant.

There were no significant changes in the latex fixation test or in antinuclear factor as the trial progressed.

Serum copper values fell significantly as expected in the patients receiving penicillamine as compared with the C group at both 12 and 24 weeks. ($P < 0.01$ and $P < 0.05$, respectively). At 12 weeks the patients in the 1200 group had significantly lower serum copper values than those receiving the smaller dose (600 group), but by 24 weeks the difference was no longer significant.

Serum zinc values showed no significant changes. SGOT, alkaline phosphatase, and serum bilirubin estimations, made on all patients frequently throughout the trial, showed no evidence of variation outside normal limits.

ADVERSE REACTIONS AND WITHDRAWALS FROM THE TRIAL

Information on adverse reactions was elicited by use of a standard nonleading question and all symptoms which were not clearly unrelated to treatment were so classified (Table VII).

The most frequently encountered adverse reaction was loss of or abnormality of sense of taste, occurring in 8 of 34 patients in the 600 group and 11 of 45 in the 1200 group, a frequency of 24% in each case. Rashes (or sometimes pruritus without a rash) occurred in 15% and 20% of the two treated groups, respectively, and dyspepsia, nausea, or vomiting in 21% and 20%, respectively. The frequency of this last symptom group was 20% in the C group, but in those receiving penicillamine it frequently accompanied loss of taste and constituted a reason for withdrawal from the trial.

One patient in the 600 group developed neutropenia (absolute count $294/\text{mm}^3$) and there were 3 in the 1200 group with mild thrombocytopenia. Two of these also had some neutropenia (absolute counts 1050 and 1728). All were withdrawn from the trial and their blood counts rapidly returned to normal after stopping penicillamine. Abnormalities of taste (often with nausea and vomiting), rashes, and blood dyscrasias were the cause of all but two withdrawals due to adverse reactions. One exception was withdrawn from the 600 group because of proteinuria (100 mg/100 ml) and the other from the 1200 group due to diarrhoea and buccal ulcers within a day or two of completing the trial.

Four patients were withdrawn for other reasons. One patient in the 1200 group developed pernicious anaemia and another in the same group could not continue in the trial because of transport difficulties. One patient in the 600 group was withdrawn because of a pyrexial illness, probably influenza, and the remaining patient in the C group developed atrial fibrillation and congestive cardiac failure. Two other patients in the C group died of myocardial infarction during the trial.

Discussion

This study confirms previous findings (Multicentre Trial Group, 1973; Day and others, 1974) that D(-)penicillamine is of therapeutic value in rheumatoid arthritis. Doses of both 600 and 1200 mg daily added to standard treatment produced statistically significant improvement in relief of pain, grip strength, ESR, and haemoglobin. Improvement usually began between 4 to 8 weeks after starting treatment, but was often not complete until at least 12 weeks or more had elapsed. Duration of disease did not appear to affect therapeutic response and there was no evidence of significant change in x-rays of the hands or feet, or in the size or number of rheumatoid nodules during the 6 months of the trial.

The type and extent of adverse reactions were similar to those reported by other authors. Three patients in C group complained of abnormality of taste or of a 'metallic' taste, but it is likely that these

symptoms were related to discussion with other patients in the trial than to the daily dose of 12 mg penicillamine the group was receiving. One patient only was withdrawn because of proteinuria, probably related to the relative shortness of the trial since immune-complex nephropathy is often a later complication. However, there were only two other patients with mild proteinuria, a total frequency of 2.5%.

Significant overall dosage-related effects occurred not only with regard to the extent of improvement and the number of patients improving, but also to the frequency of adverse reactions. At no time, however, did the differences between the high and low dose groups attain statistical significance when analysed separately. It is therefore necessary to examine the therapeutic implications of this situation.

Table VI shows that 70% of patients in the 1200 group improved (taking grip strength as representative of the 3 clinical parameters assessed in this way) compared with 56% of those in the 600 group. The standard error of the difference between the percentages is 13% and therefore, with confidence limits of 95%, the true difference lay between -12% and +40% ($14 \pm 2 \times 13$). A similar calculation for the number of patients suffering adverse reactions in the two groups gave -9% to +43%. The implications of this are that a change in dosage from 600 to 1200 mg daily could produce a result varying from a small decrease to large increase both in improvement and adverse reactions, though the extremes of these changes would not of course necessarily correlate with each other. Furthermore it must be recalled that the figures given in Table VI represent patients who were able to complete 24 weeks' treatment. If we include as 'treatment-failures' all those who withdrew because of adverse reactions, the percentages become 41% and 42% improved in the 600 and 1200 groups, respectively. In fact not all of these were true 'failures' since many had shown clear evidence of improvement before being withdrawn. For the overall clinical management of the individual patient, however, the comparison is valid.

The conclusions from this study are that the initial dose of D(-)penicillamine should be as low as possible, that adequate time (4-8 weeks) should be given for clinical improvement to take place, and that increases in dosage should be made slowly, by small increments and with due awareness that they may bring an increased frequency of adverse reactions. D(-)penicillamine appears to be a practical treatment for early as well as late rheumatoid arthritis.

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the increasing sophistication of way of life (Popert and Hewitt, 1962; Rose and Prior, 1963). A further step will be to study the relationship between SUA concentrations and common disease processes, which also have a changing prevalence. Similarly, potential environmental determinants of SUA concentrations will be selected for scrutiny to establish the extent of their influence upon this course of events.

The earlier surveys of rural and urban African communities were made under the aegis of Professor Louis

Solomon, Department of Orthopaedic Surgery, University of the Witwatersrand, Johannesburg.

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Correction: 'Synthetic D(-)penicillamine in rheumatoid arthritis. Double-blind controlled study of a high and low regimen.' By Dixon *et al.* *Annals*, October 1975, **34**, 416.

Page 416, column 2, line 10 should read, 'The material contains less than 0.3% of the optical isomer, L(+)penicillamine, which is regarded as toxic.'