D-penicillamine withdrawal in rheumatoid arthritis

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SUMMARY Thirty-eight patients with rheumatoid arthritis in remission on penicillamine were entered into a prospective, randomised, placebo controlled study to determine the effects of gradual penicillamine withdrawal, to find a serological marker capable of predicting relapse, and to assess the effects of reintroduction of penicillamine. 80% of patients attempting gradual penicillamine withdrawal flared. There was no single serological marker capable of predicting outcome consistently. Decreasing SH levels were highly specific for recurrence of active synovitis but were insensitive. Reintroduction of penicillamine was successful. The implications of these findings, particularly concerning duration of therapy with disease modifying drugs, are discussed.

The efficacy of D-penicillamine (penicillamine) in rheumatoid arthritis (RA) has been demonstrated in many double-blind prospective studies.^{1–4} However, complete remission for at least 2 years, defined by no joint symptoms, normal laboratory tests, and withdrawal of all drugs, occurs in only 4% of patients on penicillamine.⁵ Advice given to patients with RA who have a sustained remission on penicillamine is conflicting. Do such patients attempt to reduce their dose of penicillamine gradually or to continue treatment indefinitely? Indeed, is the maintenance of the remission due to the action of the drug itself or to the natural history of rheumatoid arthritis?

Many rheumatologists feel that, as the incidence of side effects such as thrombocytopenia⁶ and proteinuria⁷ is greater on higher doses of penicillamine, gradual reduction of the dose of the drug should be attempted. Anecdotal evidence suggests that on withdrawing penicillamine a recurrence of inflammatory activity is likely and that reintroduction of the drug is less successful.^{8,9}

There have been no published trials assessing the effects and risks of gradual penicillamine withdrawal. We therefore designed a prospective, randomised, placebo controlled study. Our objectives were to determine the effects of gradual withdrawal of penicillamine in patients with rheumatoid arthritis in remission, to find a serological marker that could predict relapse and therefore guide future withdrawal attempts, and thirdly to assess the results of the reintroduction of penicillamine.

Patients and methods

Four hundred and forty consecutive patients with RA on penicillamine for a minimum of 12 months were reviewed. Of these 440 patients only 40 (9%) with definite or classical RA¹⁰ were found to be in remission. These 40 patients were then followed up prospectively for a further 6 months to confirm the presence of remission. Remission was defined as the absence of clinically active joint disease. Joints were considered active if they were tender to palpation or at extremes of motion, or if there were soft tissue swelling or effusion. Conversely, we defined relapse as recurrence of active joint disease even if only one joint became involved.

Thirty-five of the patients fulfilled the requisite number of ARA criteria for complete clinical remission¹¹ (13 patients had 6 criteria and 22 had 5 criteria). Five patients had 4 criteria. These last 5 patients had joint pain of a mechanical nature and morning stiffness exceeding 15 minutes but less than 30 minutes.

At six months 38 patients remained in remission, 2 patients being excluded because of recurrence of active joint disease. These 38 patients represent 8.6% of our RA patients on penicillamine. At 6 months the 38 patients were randomly allocated to one of 2 groups: one group to remain on the same dose of penicillamine (control group), the other group to withdraw the drug by 125 mg/month by substituting dummy tablets. We selected a reduction rate of 125 mg/month because that was most widely practised by several rheumatologists interviewed.

Both groups were closely matched with respect to age, sex, duration, and type of disease, duration of

penicillamine therapy, and dosage (Table 1). Non-steroidal anti-inflammatory drugs and analgesic medications were continued unchanged throughout the study. The study was explained to all patients and their consent obtained. Ethical committee approval was granted.

Both groups were followed up at monthly intervals for a further 12 months. At each visit the patients were assessed at the same time each day by an observer unaware of the patients' treatment group, who recorded duration of morning stiffness, grip strength, total proximal interphalangeal joint circumference, and the patient's and observer's impression on a 5-point scale (much worse, worse, same, better, much better).

LABORATORY INVESTIGATIONS

Plasma viscosity was measured by capillary viscometry,¹² the normal range being 1.50–1.72 cp. C-reactive protein (CRP) was determined with a Hyland Disc 120 automated protein analyser (laser nephelometer) supplied by Hyland Division Travenol Laboratories (normal values <12 mg/l).

IgM and IgG rheumatoid factors were detected by a nephelometric method, and serum immune complexes were assayed in a ¹²⁵I-Clq binding assay (Clq BA) as described by Zubler and Lambert.¹³

Complement components (C3 and C4) and immunoglobulins were measured by radial immunodiffusion.

All sera for measurement of CRP and Clq BA were stored at –20°C and –70°C respectively and tested in a single batch.

SERUM SULPHYDRYL ASSAY (SH)

Serum samples were stored at –20°C before use. SH groups react with Ellman's reagent 5,5' dithiobis (2 nitrobenzoic acid) (DTNB)¹⁴ to form a yellow product which may be determined spectrophotometrically at 440 nm. An aliquot of serum (50 µl) was diluted with 750 µl 0.1 M phosphate buffer pH 7.4 and reacted with 200 µl freshly prepared DTNB solution (2 mM) for 5 minutes at 37°C. The absorbance at 440 nm was then measured against a serum blank in a Cecil CE292 spectrophotometer. The reading was converted to serum SH concentration (in µmol l⁻¹) by reference to a calibration curve obtained from known amounts of reduced glutathione in the assay system. Daily variations in serum SH levels have been assessed previously, with no significant changes in serum SH.

Statistical methods used were Wilcoxon's rank sum tests for paired nonparametric data and paired Student's *t* test for parametric data.

Results

Of the 19 patients continuing the same dose of D-penicillamine (control group) 17 remained in remission. Of 19 who reduced dosage 15 flared from 2 to 7 months (mean 3.3) after beginning withdrawal

Table 1 Patients at allocation

	Same dose (n=19)	Reducing dose (n=19)
Sex	12F 7M	10F 9M
Age	58.4 years	55.8 years
Duration of RA	10.9 years	11.6 years
Duration of DPA therapy	3.7 years	3.3 years
Median dose	500 mg	500 mg
Seropositive	13	11
Extra-articular features	6	7
Functional class (median)	2	2
Erosive changes on X-ray	14	15

Fig. 1 Results of treatment.

and 4 remained in remission 9 to 12 months after complete withdrawal (Fig. 1). Ten of the 15 patients who flared developed polyarticular synovitis, while only five had a relapse affecting only one joint.

The results were analysed to determine whether or not any serological markers predicted relapse. For this purpose the 2 patients who flared despite continuation of penicillamine and the 4 patients in remission after penicillamine withdrawal were excluded, as it was thought that these patients were unlikely to demonstrate that marker. In determining the sensitivity and specificity of these possible markers all 38 patients were analysed. In the withdrawal group there was no significant change in haemoglobin, platelet count, plasma viscosity, immunoglobulin levels, or rheumatoid factor at or prior to the time of relapse. The Clq BA was normal in both groups of patients and remained normal throughout the study, even at the time of relapse in the withdrawal group. The mean CRP level increased in the withdrawal group (Fig. 2) one month before relapse, but this only became statistically significant one month and 3 months after clinical relapse. The results of serum SH levels are shown in Fig. 3. The mean SH levels were reduced in the withdrawal group at 3 months before

relapse but only became significant at one month before relapse. However, the mean SH level was at the lower limit of the normal range at the time of relapse, because 3 patients had SH levels greater than $500 \mu\text{mol/l}$ at the time of relapse. These 3 patients denied resuming penicillamine surreptitiously and did not appear to respond prematurely to reintroduction of penicillamine. The SH levels remained normal in the 4 patients who remained in remission following complete withdrawal of penicillamine. Only 6 patients had a consistent pattern of declining SH levels, including one patient who flared in the same dose group. Sensitivity was therefore 6/17 (35%), but specificity was 95%, as there was only one false positive. Similarly the CRP test was insensitive (47%) but more specific (81%).

REINTRODUCTION OF PENICILLAMINE

All patients who had a recurrence of disease activity on withdrawal were asked to resume their former dose of penicillamine. Ten of the 15 patients who flared asked to resume penicillamine because of generalised joint activity. Thirteen of the 15 responded to their former dose within 4 months, having achieved a complete clinical remission. Two

Fig. 2 Mean C-reactive protein. The vertical bars represent ± 1 SD about the mean at each time point. The 2 groups differ significantly at one month and at 3 months after clinical relapse ($p < 0.05$). The shaded area represents the normal range (mean ± 2 SD).

Fig. 3 Mean serum SH levels. The vertical bars represent ± 1 SD about the mean. The 2 groups differ significantly at one month prior to relapse ($p < 0.01$). In the withdrawal group the difference between the mean at one month before relapse and the 3 baseline values obtained prior to allocation was significant ($p < 0.01$).

required an increased dose but eventually responded to the higher dose. However, 6 months after relapse the CRP had not returned to normal in 5 patients.

Discussion

The patients chosen for the study were a selected group of patients with RA who were in remission on penicillamine, with no toxicity. They were, by selection, a group with severe RA who had done well on penicillamine. This study was designed with 3 specific goals.

Firstly, we have shown that 80% of our patients in remission attempting gradual penicillamine withdrawal flared. As the temporal relationship between withdrawal and recurrence of active synovitis was so strong (the probability of this occurring by chance alone was 4.73×10^{-5} , exact probability test) penicillamine withdrawal can be implicated in the cause of the recurrence. This suggests that penicillamine continues to suppress disease activity many years after successful induction of remission and that prolonged spontaneous remission occurs infrequently in this group of patients with RA. However, 4 patients remain in remission after complete withdrawal of

penicillamine and presumably represent examples of spontaneous remission. This sustained benefit from penicillamine is similar to the experience obtained with gold therapy, where prolonged maintenance treatment is advisable.¹⁵⁻¹⁷

Secondly, we found no single serological marker that predicted outcome consistently. The serum SH levels were the best guide to predicting a clinical relapse but were too insensitive to be of routine clinical assistance. The SH levels are not an indirect assay of blood D-penicillamine levels, as the SH levels remained normal in the 4 patients who withdrew penicillamine therapy completely but remained in remission. Also the plasma concentration of D-penicillamine is generally less than $10 \mu\text{g/ml}$ (approximately $5 \times 10^{-5} \text{ mol/l}$) in rheumatoid patients receiving 750 mg daily in divided doses.¹⁸ Even if all this penicillamine were free (i.e., unbound), this still represents less than 10% of the total serum SH level. However, at least 80% of penicillamine is bound to albumin through the SH group.¹⁹ The finding of depressed SH levels before clinical relapse is apparent suggests that the mechanism responsible is already well established in these

patients. There is evidence to suggest that the reaction responsible for lowering serum SH is oxidation caused by hydrogen peroxide and other reactive oxygen derived species released by activated phagocytes.²⁰ Depressed serum SH levels may indicate stimulated phagocytic cells, particularly neutrophils releasing oxygen-free radicals and other tissue damaging species, and time is required before the clinical effects of this are seen. Five of the 6 patients with declining SH levels had a polyarticular flare, so that such a pattern may predict the severity of the relapse and explain the insensitivity of the test.

Thirdly, we found that reintroduction of penicillamine after it had been reduced or withdrawn was successful. Not all patients responded to the same dose of penicillamine, but all patients regained a complete clinical remission, although the CRP had not returned to normal in 5 patients. In this respect penicillamine is different from gold, where reintroduction of gold therapy after withdrawal or previous courses is less successful.²¹ These differences, however, are probably explained by selection of patients and differences in design study. Our patients were selected because they were in remission for at least 18 months (12 months retrospectively and 6 months prospectively) and had done extremely well on the drug.

The study suggests that indefinite treatment with penicillamine, provided no toxicity occurs, is advisable. 20% of the patients attempting penicillamine withdrawal remained in remission 9–12 months after stopping penicillamine but 80% flared, of whom two-thirds had polyarticular synovitis and asked to resume their former therapy. We do not believe that the benefits profiting the minority justify putting the majority at risk of developing a severe flare. However, we realise that this is contentious, as penicillamine therapy must be continually monitored, creating inconvenience and utilisation of time and resources for patients and medical staff. It remains possible that a slower reduction schedule (e.g., over 3 years or 125 mg every 3 months) might be successful.

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