Penicillamine Treatment of Rheumatoid Arthritis with a Single Daily Dose of 250 mg

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The efficacy of penicillamine in the treatment of rheumatoid arthritis was first demonstrated in sequential studies in which patients served as their own historical controls (Jaffe 1965, 1970). These observations were subsequently confirmed in a double-blind controlled trial which demonstrated the effectiveness of penicillamine against placebo in the treatment of severe rheumatoid arthritis (Multicentre Trial Group 1973). Additional trials have shown the drug to be comparable in efficacy to gold (Huskisson *et al.* 1974), and azathiaprine (Berry *et al.* 1976) in suppressing the signs, symptoms and laboratory manifestations of rheumatoid arthritis.

The major factor limiting the usefulness of penicillamine has been the high incidence of side-effects and toxic reactions. In an effort to influence the therapeutic ratio of the drug favourably, regimens with slower increments in dosage and lower maintenance levels have been employed with some success (Day *et al.* 1974, Jaffe 1975). In a recently published controlled trial, it was found that a daily maintenance dose of 600 mg was equal in efficacy to that of 1200 mg, with a decrease in incidence of side-effects in the patients receiving the lower dosage (Dixon *et al.* 1975).

It is the purpose of this presentation to describe the preliminary results obtained in a group of 6 patients with rheumatoid arthritis who were treated for periods up to one year with a single daily dose of 250 mg of penicillamine. These patients met the accepted criteria for penicillamine therapy, and represented both early and moderately advanced disease. Previous treatment with penicillamine was an absolute contra-indication to the study. The single daily dose was administered approximately 1½ h after the evening meal, and was taken with water. No other medications were permitted within 1½ h before or after the single penicillamine dose. Steroids, analgesics and nonsteroidal anti-inflammatory drugs could be taken as required throughout the day and at bedtime.

In this group of 6 patients, there was unequivocal clinical and laboratory response to the drug in 4. There were, however, certain noteworthy differences when the response of these patients was compared to that of patients who were treated with the conventional graduated dosage regimen to maintenance levels of 750 to 1500 mg daily. Stabilization of disease activity, which is generally achieved between the eighth and twelfth week with the higher doses, was delayed with the low dose programme. Sixteen to 24 weeks elapsed before deterioration in clinical status was halted, approximately a doubling of the latent period. Improvement then progressed in a manner which did not appear to differ from that previously observed, except that the rate of improvement was slower. Correction of the anæmia and decrease in the ESR occurred at the expected time, but reductions in serum rheumatoid factor were less dramatic and took up to one year to assume significance. With respect to the side-effects encountered, one patient developed moderate and transient hypogeusia and another had mild pruritus, neither of which required cessation of the drug. There were no hæmatological or renal complications; however, the period of observation is far too short and the number of cases too few to permit meaningful comparison with previous trials.

The results of these preliminary observations are sufficiently encouraging to warrant a controlled trial comparing a single daily penicillamine dose of 250 mg as described above, with the standard, higher dosage regimens currently employed. It is only by the performance of such a study that the minimum effective dose of penicillamine can be determined. If, as earlier experience indicates, certain of the untoward effects of the drug are dose-related, then a more favourable therapeutic ratio may be anticipated provided that efficacy is not proportionately diminished.

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