Continuous and intermittent levamisole

A controlled trial

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SUMMARY A double-blind comparative trial showed that intermittent levamisole therapy (150 mg daily for 3 days of each week) was as effective as continuous therapy (150 mg daily) in rheumatoid arthritis and with slightly fewer side effects.

Levamisole has been shown to be effective in rheumatoid arthritis, using a continuous treatment regimen (Huskinson *et al.*, 1976; Rosenthal *et al.*, 1976). Intermittent therapy might be even more effective if enhancement of cell-mediated immune responses was important in the mode of action of the drug. Thus Verhaegen *et al.* (1973) found intermittent therapy more likely than continuous therapy to restore skin reactivity to DNCB; Veys *et al.* (1976) reported that intermittent therapy was effective in rheumatoid arthritis. In this study the two regimens, continuous and intermittent therapy, were compared.

Methods

Twenty-four patients with rheumatoid arthritis were admitted to a double-blind trial, 12 receiving continuous levamisole therapy (150 mg daily) and 12 receiving intermittent levamisole therapy (150 mg daily on 3 consecutive days of each week). Before the start of the study they were stabilised on an optimum anti-inflammatory regimen. No patients had received penicillamine or other slow acting drugs within the previous 6 months.

Levamisole was given in an initial dose of 50 mg daily (either 3 days of the week or every day) and increased by 50 mg at fortnightly intervals to a dose of 150 mg. All patients were given 2 bottles of tablets. The first was labelled 'Monday, Tuesday, Wednesday' and contained active tablets; the second was labelled 'Thursday, Friday, Saturday, Sunday' and contained either active tablets or identical placebo. Patients were allocated to one or other treatment at random.

Measurements made before the start of treatment and again after 3 and 6 months' treatment included

pain using a visual analogue scale (later divided into 20), duration of morning stiffness, articular index (Ritchie *et al.*, 1958), proximal interphalangeal joint circumference (Boardman and Hart, 1967), erythrocyte sedimentation rate, rheumatoid factor titre using the latex test, immunoglobulins (IgG, IgA, IgM), and antinuclear factor.

Weekly measurements of pain relief, using a visual analogue pain relief scale, and duration of morning stiffness were made by the patients. Blood samples were taken at regular intervals for routine haematological and biochemical tests. Side effects were elicited at each visit in response to the question, 'Have the tablets upset you in any way?'

Statistical methods

Student's *t* test and the Mann Whitney U test were used to compare differences between changes in the treatment groups. Paired *t* tests and the Wilcoxon test were used to test changes within the treatment groups.

Results

Initial clinical measurements are shown in Table 1. There was no significant difference between the groups in any measurement. 22 patients completed 6 months' treatment with levamisole. Both treatment

Table 1 Mean initial values for clinical measurements

	Pain	Duration of morning stiffness (min)	Articular index	Joint size (mm)	ESR (mm/h)
Continuous	12.6	52	15.7	604.4	44
Intermittent	11.9	65	13.4	583.3	56

groups showed a statistically significant improvement after 6 months. None of the measurements showed any difference between the groups (Table 2). Pain relief was gradual, maximal at 6 months (Fig. 1), and the time course of the response was identical in the two groups. There was no significant difference between changes in the titre of rheumatoid factor in the two groups.

Side effects (Table 3) led to withdrawal of treatment in one patient in each group. One was withdrawn from the intermittent levamisole group with a lupus-like syndrome after 7 weeks of treatment. He developed a photosensitive rash which had histological characteristics compatible with systemic lupus erythematosus. There was lymphocytic infiltration around vessels in the skin and immunofluorescent staining showed deposits of IgM, IgG,

and complement in the superficial dermis. The titre of antinuclear factor rose from 1/100 to 1/500. The rash resolved rapidly when treatment was stopped. One patient was withdrawn from continuous therapy after 4 weeks because of agranulocytosis. Her neutrophil count was $0.175 \times 10^9/l$ and bone marrow showed arrest at the promyelocyte stage. She recovered rapidly after stopping levamisole. Side effects in both groups included nausea, mouth ulcers, rash, lethargy, and disturbed taste. These were slightly more frequent in the continuous group than the intermittent group, but the difference was not statistically significant. In the intermittent group one patient became neutropenic (neutrophil count $0.5 \times 10^9/l$) but recovered while continuing treatment, and in another the neutrophil count fell from 4.8 to 1.8 cells $\times 10^9/l$ and remained at about this level.

Changes in neutrophil and lymphocyte counts showed no correlation with pain relief. There were statistically highly significant rises in haemoglobin levels in both groups and falls in platelet counts, though no one became thrombocytopenic. There was a slight but statistically significant rise in the mean level of serum creatinine in both groups though not exceeding $35 \mu mol/l$ (0.4 mg/100 ml) in any patient, and a slight fall in the phosphate level. Immunoglobulin levels fell in both groups. 6 patients in the continuous group and 4 in the intermittent group showed rises in the titre of antinuclear factor. When the groups were combined, the rise in antinuclear factor was statistically highly significant. Mean changes in some laboratory values are shown in Table 4.

Discussion

Intermittent levamisole therapy has proved to be as effective as continuous therapy in the treatment of rheumatoid arthritis. That there were fewer side effects suggests an advantage in intermittent therapy. In any case, it is pointless to give more of a drug than is necessary to achieve a particular response.

Table 2 Mean changes after 6 months' treatment with levamisole

	Pain	Duration of morning stiffness (min)	Articular index	Joint size (mm)	ESR
Continuous	-7.2	-33	-8.5	-20.3	-19
Intermittent	-6.5	-47	-7.9	-17.9	-34

Note: There was no significant difference between the groups. All measurements showed a significant improvement.

Fig. Mean weekly pain relief scores showing time course of response

Table 3 Total incidence of side effects

	Continuous	Intermittent
Neutropenia	1	2
Nausea	5	1
Mouth ulcers	4	2
Rash	2	3
Lethargy	1	2
Taste disturbance	1	2

Table 4 Mean changes after 6 months' treatment with levamisole

	Continuous	Intermittent
Hb	+1.1	+1.2
Platelets	-124	-102
White cell count	-0.4	-1.0
Neutrophils	-0.06	-0.32
Lymphocytes	-0.28	-0.47
Creatinine	+15	+5
Phosphates	-0.09	-0.19
IgG	-4.27	-5.54
IgA	-1.09	-1.22
IgM	-0.41	-0.22

The lowest effective dose of levamisole has not yet been established and the use of even smaller doses may lead to a further reduction in the incidence of side effects. Intermittent therapy is still potentially dangerous and in view of the case of neutropenia which occurred, still requires the most careful supervision.

References

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