A thermographic and clinical comparison of three intra-articular steroid preparations in rheumatoid arthritis

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SUMMARY We have compared three intra-articular steroid preparations in a double blind study on 30 patients with rheumatoid arthritis and bilateral synovitis of the knees. One knee was injected with 1.0 ml of either prednisolone t-butyl acetate, methyl prednisolone acetate, or triamcinolone hexacetonide, and the patients were followed up for 6 weeks with regular clinical and thermographic assessments. Thermographic improvement was seen with all 3 drugs but was greatest initially and longest lasting with triamcinolone. No significant systemic improvement was seen with any drug after a single injection, though all 3 steroid preparations suppressed endogenous cortisol.

Intra-articular steroid injections have been used in rheumatoid arthritis since 1951 when Hollander *et al.* (1951) first used hydrocortisone. Prednisolone followed (Rothermich and Phillips, 1957), and more recently both methyl prednisolone and triamcinolone have become available. In spite of the wide variety of proprietary brands there have been few comparative studies to advise on choice. Baine *et al.* (1967) found significantly greater improvement with methyl prednisolone than with prednisolone, and Dixon *et al.* (1972) found that triamcinolone produced marginally greater benefit with fewer local side effects than prednisolone acetate, but neither of these studies used an objective assessment of inflammation.

A previous study in this unit (Esselinckx *et al.*, 1978) compared 3 intra-articular analogues of prednisolone (prednisolone acetate, prednisolone pivalate, and prednisolone t-butyl acetate) at 2 dosage levels, using infrared quantitative thermography to measure inflammation. Prednisolone t-butyl acetate produced a significantly greater and more sustained anti-inflammatory effect than the other 2 compounds. This was not significantly improved by increasing the dose from 50 mg to 100 mg, and since the higher dose caused more suppression of endogenous cortisol the lower dose was judged the better one.

We therefore decided to compare prednisolone

t-butyl acetate with 2 other synthetic steroid preparations that on pharmacological grounds might be expected to be more efficacious than prednisolone. These were methyl prednisolone acetate and triamcinolone hexacetonide. We limited the comparison to intra-articular injections of 1 knee in patients with classical or definite rheumatoid arthritis (ARA criteria) and used the lowest dose recommended by the manufacturers for this joint and disease. The study was double blind, and thermography provided an objective assessment of inflammation. Patients were followed up for 6 weeks, and serial plasma cortisol levels were performed.

Many authors have suggested that a single intra-articular injection may produce systemic improvement. We therefore performed serial clinical assessments of all joints and followed the full blood count and plasma viscosity throughout the study.

Patients and methods

Thirty outpatients or inpatients with classical or definite rheumatoid arthritis (ARA criteria) were allocated at random to 3 groups. Patients taking oral steroid preparations or immunosuppressive drugs were excluded, but patients receiving gold or D-penicillamine were included if dosage had been stable for 3 months. Patients who had received intra-articular or systemic steroids in the previous 3 months were excluded, and a prerequisite for entry was that the disease affected both knees symmetrically. Drug therapy remained constant throughout the study.

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STEROID PREPARATIONS

A single intra-articular injection was given to 1 knee, chosen at random, without knowledge of the preparation. Synovial fluid was aspirated prior to injection but the joint was not then reaspirated. The dosages used were prednisolone t-butyl acetate (Codelcortone-TBA), 20 mg in 1 ml, 10 patients; methyl prednisolone acetate (Depo-Medrone), 40 mg in 1 ml, 10 patients; and triamcinolone hexacetonide, (Lederspan), 20 mg in 1 ml, 10 patients. The steroid preparations were undiluted and not mixed with local anaesthetic.

ASSESSMENTS

Patients attended a special clinic on days 0, 2, 4, 7, 14, 28, and 42. Thermograms of both knees were carried out before injection on day 0 and at the same time of day on each subsequent visit under standardised conditions as described by Ring (1975). The thermographic index (TI) of the injected and non-injected knee was recorded by the method of Collins *et al.* (1974) and the change in TI from the pre-injection readings calculated. Articular index (Ritchie *et al.*, 1968), grip strength, global pain score on a visual analogue scale, and duration of morning stiffness were recorded on days 0, 7, 14, 28, and 42.

INVESTIGATIONS

Full blood count and plasma viscosity were performed on days 0, 14, and 42. 10 ml of venous blood for cortisol estimation was collected into heparinised tubes on days 0, 2, 4, 7, 14, and 28. Plasma was then separated and stored at -20°C before estimation.

Cortisol estimations were performed by the fluorimetric method of Mattingly (1962). The cortisol was extracted from plasma by mixing 2.0 ml with 15.0 ml dichloromethane and centrifuging the mixture at 2000 rpm for 10 minutes at 18°C . The dichloromethane extract was decanted and 10.0 ml transferred to a smaller tube. The fluorescence reagent was prepared by mixing 70 ml concentrated sulphuric acid with 30 ml ethyl alcohol. The cortisol extract was shaken vigorously with 5.0 ml of fluorescence reagent for 20 seconds and the supernatant dichloromethane pipetted off. The acid extract was then transferred to a fluorimetry cell and fluorescence at 525 nm read thirteen minutes after mixing using an exciting light of 472 nm wavelength. The results were calibrated with a reagent blank and compared to a series of standard cortisol solutions estimated by the same method. Cortisol levels were then subtracted from the preinjection level.

STATISTICS

Student's *t* test was used throughout the study.

Results

CLINICAL ASSESSMENTS

There were no significant differences between any of the 3 groups for any parameter before the injection. The articular index showed no significant improvement in any group, the most improvement being obtained with methyl prednisolone at 14 days ($P=0.1$). Morning stiffness also showed no significant improvement in any group, triamcinolone at 7 days ($0.5 > P > 0.1$) being best. For pain score there was a significant improvement in the triamcinolone group at 7 days ($0.05 > P > 0.02$), though this was not maintained at 14 days ($0.5 > P > 0.1$). No other group showed improvement. Grip strength showed no significant changes in any group, the greatest improvement being with triamcinolone at 28 days ($P > 0.5$). Differences between groups were not significant at any time.

LABORATORY ASSESSMENTS

The 3 groups were initially well matched with respect to full blood count and plasma viscosity. No significant changes were seen in haemoglobin or white blood count at any time, either within or between groups. Plasma viscosity fell slightly by 6 weeks in all 3 groups, the fall being greatest with prednisolone t-butylacetate, though this was not significant ($0.5 > P > 0.1$).

THERMOGRAPHIC ASSESSMENTS

The improvement in injected knees for the 3 groups is shown in Fig. 1. All groups improved with the greatest change at 1 week. Improvement was subsequently lost, though knees injected with triamcinolone maintained their improvement at 6 weeks, when knees injected with the other 2 preparations had returned to their preinjection value. Moreover, the improvement with triamcinolone was more pronounced than with the other preparations. As to change within groups, the triamcinolone improvement was highly significant at 7 days ($P < 0.001$) and significant at 4, 14, and 28 days. Change with methyl prednisolone was significant at 2 days ($0.02 > P > 0.01$) and 4 days; change with prednisolone t-butyl acetate significant only at 4 days ($0.02 > P > 0.01$).

The improvement in the contralateral non-injected knees is shown in Fig. 2. Although the knees of patients on methyl prednisolone and prednisolone t-butyl acetate showed no change, the non-injected knees of those on triamcinolone showed an improvement of similar magnitude to the knees injected with methyl prednisolone, though this improvement did not reach significant levels.

PLASMA CORTISOL ESTIMATIONS

The fall in endogenous plasma cortisol in the 3

Fig. 1 Mean fall in thermographic index (TI) of injected knees from groups of patients treated with prednisolone t-butyl acetate, methyl prednisolone acetate, and triamcinolone hexacetonide. Bars represent standard error of the mean.

Fig. 2 Mean change in thermographic index of the non-injected knees from groups of patients treated as in Fig. 1. Bars represent standard error of the mean.

groups is shown in Fig. 3. Adrenal suppression occurred with all 3 drugs, being maximal by 2 or 4 days and being most pronounced in those patients receiving prednisolone t-butyl acetate.

Discussion

Although many patients showed modest clinical improvement after intra-articular injection, we found no significant systemic improvement with any of the steroid preparations used. A controlled study would be required to ascertain whether the minor changes seen resulted from steroid therapy or whether they arose because of regular clinical follow-up.

Thermography showed clear differences between groups of injected knees. Improvement occurred with all 3 drugs but the pattern seen with triamcinolone differed in 2 respects: the initial maximum improvement was greater, and the improvement

was maintained to the end of the study at 6 weeks, a stage when the other groups had reverted to normal. Improvement with triamcinolone reached a greater level of significance than with the other 2 drugs.

Thermography also revealed differences between groups of non-injected knees, there being an improvement in the triamcinolone group not seen with the other 2 steroid preparations. The improvement was comparable in magnitude to the injected knees of the methyl prednisolone group.

It is not clear why injected and non-injected knees behaved differently according to the steroid preparation used. The injected knee was chosen at random and there was no significant initial difference between knees (mean TI injected knees/non-injected knees = $4.71/4.09$). When exogenous plasma steroid levels are measured (Esselinckx *et al.*, 1978) it can be shown that prednisolone analogues enter the systemic circulation from the joint very quickly.

Fig. 3 Mean fall in endogenous plasma cortisol for the 3 groups of patients treated as in Fig. 1. (Conversion to SI: $1 \mu\text{g}/100 \text{ ml} = 27.6 \text{ nmol/l}$.)

With methotrexate, a drug for which adequate and sensitive bioassays exist, the drug is always present in synovial fluid of 1 knee half an hour after injection into the synovial cavity of the opposite knee (Bird *et al.*, 1977). It is therefore possible that improvement of the non-injected knee in patients injected with triamcinolone represents a systemic effect of this drug, even though this was not reflected in the global clinical assessments. One possible explanation for this is that the patients were selected because of bilateral knee synovitis and their other joints were less active. Why methyl prednisolone and prednisolone t-butyl acetate did not also show this systemic effect is uncertain, and further studies using direct assays of these drugs are required to see if they leave the joint at different rates. Esselinckx *et al.* (1978) have suggested that systemic effect is a function of steroid solubility. In their comparison of 3 prednisolone analogues they found the least change in the contralateral knee of patients injected with prednisolone t-butyl acetate, the least soluble of the 3 prednisolone salts.

In this study the plasma cortisols do not help to elucidate this. They show adrenal suppression with all 3 drugs, initially most marked with prednisolone t-butyl acetate and longest lasting with methyl prednisolone. However, it is still possible that triamcinolone is more soluble than the other 2 drugs,

since it may have caused a large early cortisol suppression not seen in this study, in which cortisol estimations were not performed in the first 24 hours after injection. This might explain its significant action in the non-injected knee.

On the basis of the lack of cortisol suppression at 4 weeks and its longer duration of action, triamcinolone appears to have advantages over the other 2 drugs in rheumatoid synovitis in the dosages that we tested.

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