A COMPARISON OF PLASMA METHYLPREDNISOLONE CONCENTRATIONS FOLLOWING INTRA-ARTICULAR INJECTION IN PATIENTS WITH RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

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Abstract:
Plasma concentrations of methylprednisolone following intra-articular injection were measured in rheumatoid arthritis and osteoarthritis patients. While substantial plasma concentrations were seen in both groups of patients there was no significant difference in the rate or extent of absorption of methylprednisolone from osteoarthritic or rheumatoid knees. This study suggests that it is the dissolution rate of the steroid formulation rather than the characteristics of the synovial membrane which determine rate and extent of systemic absorption of methylprednisolone after intra-articular injection. (Aust NZ J Med 1983; 13: 583-586.)
Key words: Methylprednisolone, intra-articular steroids, synovial absorption.

INTRODUCTION

Intra-articular injection of corticosteroids is used extensively in the treatment of local joint inflammation in rheumatoid arthritis (RA) and osteoarthritis (OA).[1,2] Randomised controlled studies in RA[3] and OA[4] have demonstrated that intra-articular corticosteroids reduce pain and inflammation in the short term though differences from placebo are difficult to demonstrate after one month.

Absorption of corticosteroids from the synovial cavity produces both a clinical[5] and a thermographic improvement in other joints.[6] Recently Armstrong *et al.*[7] have reported serum methylprednisolone concentrations in patients with rheumatoid arthritis following intra-articular injection and have commented that it is the total surface area of synovial membrane to which the steroid is exposed that determines the degree of absorption. The hypertrophied synovial membrane of the rheumatoid joint[8] has a greater surface area for absorption than the less inflamed osteoarthritic synovial membrane. It might therefore be anticipated that there would be a more rapid and greater absorption of methylprednisolone in patients with RA compared with OA.

The trans-synovial exchange of large and small molecules has been investigated by a number of workers studying the clearance of a variety of isotopes. The mechanism of synovial clearance of molecules is complex involving active transport across the synovial membrane as well as passive diffusion across the micro-vascular endothelium and into lymphatics.[9] The clearance of $^{24}Na^{10}$ and $^{131}I^{11,12}$ is more rapid from actively inflamed rheumatoid knee joints than from normal or

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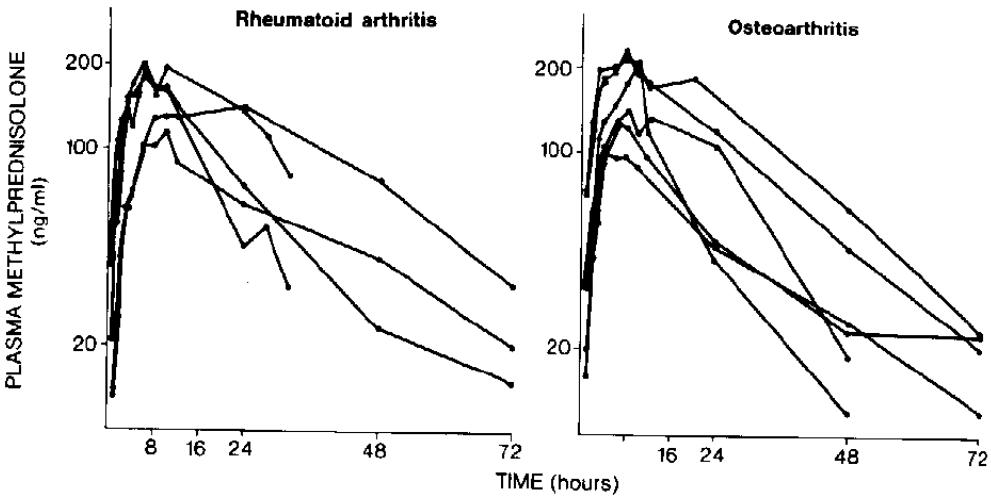

Figure 1: Plasma-concentration time profiles in RA and OA patients following intra-articular injection of 80 mg methylprednisolone (depot-medrol; Upjohn) into the knee.

osteoarthritic joints. Xenon (^{133}Xe) is also cleared more rapidly from inflamed joints reflecting an increased synovial blood flow.[13,14] The above studies have been carried out with substances already in solution and hence dissolution of the substance from its dosage form cannot be rate limiting. It is possible that the dissolution characteristics of injected corticosteroid play a major role in determining the rate and extent of systemic absorption. In view of the known difference in absorptive surfaces between OA and RA and the suggestion that synovial characteristics would determine systemic absorption we decided to compare plasma methylprednisolone levels following intra-articular injection into the knee joints of patients with RA and OA.

PATIENTS AND METHODS

Eleven patients with knee effusions (five with RA and six with OA) took part in the study. The mean age of the patients with RA was 70 years (range 64 to 77) and the corresponding value for those with OA was 69 years (range 66 to 80). Patients with RA all had active disease as manifest by ESR greater than 40, more than five swollen joints and morning stiffness in excess of one hour. The mean ESR in RA patients was 47 and the mean ESR in OA patients was 24. All patients had been admitted to hospital for treatment of a painful knee effusion and required aspiration and injection of methylprednisolone for pain relief. On each occasion the knee joint was aspirated to dryness under routine aseptic conditions and at the end of aspiration 80 mg of methylprednisolone (Depo-medrol; Upjohn) was injected into the knee. The knee was flexed and extended twice and then kept in an extended position for the next four hours. Patients remained in bed for the first four hours but then were allowed to ambulate freely. An indwelling catheter was inserted into a forearm vein for repeated blood sampling. A 10 ml blood sample was taken prior to administration of intra-articular steroid and then at half hourly intervals for three hours, hourly for a further five hours and at approximately 10, 12, 16, 24, 30, 48 and 72 hours after intra-articular injection. After blood collection, plasma was separated by centrifugation and stored at −20°C until analysed.

Plasma samples were prepared for analysis of methylprednisolone according to the method of Frey *et al.*[15] The chromatographic column, equipment and conditions employed were those described by Scott *et al.*,[16] but the mobile phase was modified to 0.5% ethanol-95% dichloromethane saturated with water. Under these conditions the retention times for dexamethasone (internal standard), cortisol and methylprednisolone were respectively 4.92, 6.25 and 8.13 minutes. Calibration curves were constructed by adding known amounts in the range of 20-400 ng of methylprednisolone to control plasma. No peaks were found in pre-dose samples which interfered

TABLE I
Pharmacokinetic Analysis of Plasma Methylprednisolone Concentrations (Mean ± Standard Error)

	Slow half-life (hours)	Area under plasma concentration-time curve (ng h/ml)	Maximum concentration (ng/ml)	Time to reach maximum concentration (hours)
Rheumatoid arthritis ($n = 5$)	18.8 ± 3.61	5366 ± 659	155.6 ± 37.9	10.4 ± 0.4
Osteoarthritis ($n = 6$)	18.32 ± 3.17	5201 ± 818	169.4 ± 34.2	8.2 ± 0.4

with those of methylprednisolone or dexamethasone. The average coefficient of variation of replicate samples ($n = 65$) was 7.2% over the range of 20-400 ng/ml. The area under the methylprednisolone plasma concentration-time curve from zero to infinite time was calculated using the trapezoidal rule,[17] the area beyond the last concentration measured being estimated as the quotient of that concentration and the slow rate constant. The slow rate constant was estimated by fitting the terminal log linear portion of the plasma concentration time curve to a mono-exponential decay equation. Statistical analysis of the differences between the two groups was carried out using the Wilcoxon rank sum test.[18]

RESULTS

The individual plasma methylprednisolone concentration-time profiles for the patients are shown in Figure 1. The pharmacokinetic data are summarised in Table 1 and show that there is no significant difference between area under the concentration-time curve, the maximum concentration achieved or the time taken to reach that maximum concentration.

DISCUSSION

Table 1 indicates that there are no significant differences between patients with OA or RA in either the rate and extent of absorption or time to reach maximum concentrations of methylprednisolone from an intra-articular injection of this formulation into the knee. This lack of difference is in spite of clearly documented differences in the rate of absorption of isotopes such as ^{22}Na and ^{131}I in RA and OA.[9] The mean slow half-life of methylprednisolone (18.5 hours) in our patients is greater than the half-life seen after an oral dose of methylprednisolone (2.6 hours) in healthy normal subjects.[19] This difference strongly supports the hypothesis that the rate of methylprednisolone release from this formulation is the rate limiting step in methylprednisolone absorption into the systemic circulation and its subsequent elimination, rather than the characteristics of the synovial membrane.

This study confirms that substantial concentrations of methylprednisolone are found systemically after intra-articular injection into RA knees and also shows that equivalent absorption occurs from OA knees. The systemic effects resulting from intra-articular corticosteroid administration are usually recognised in a generalised arthritis such as RA due to suppression of symptoms and signs of inflammation in non-injected joints but may not be as easily discernible in OA. Our study demonstrates that both groups of patients exhibit similar plasma concentration profiles following intra-articular injection and are thus equally likely to suffer systemic effects. It has been demonstrated that serum cortisol levels can be suppressed for up to one week following intra-articular methylprednisolone injection into RA knees[1] and this is also likely to occur in OA.

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