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Serum methylprednisolone levels following intra-articular injection of methylprednisolone acetate

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SUMMARY Twenty-one patients with rheumatoid arthritis received injections of either 40 mg or 80 mg of methylprednisolone acetate into one or both knee joints. Serum methylprednisolone and cortisol levels were measured at intervals up to 1 week following injection. Peak serum levels of methylprednisolone were reached at between 2 and 12 hours following injection, and increasing the injected dose resulted in correspondingly higher serum levels. Injection of 80 mg of methylprednisolone as 40 mg into each knee produced consistently higher peak serum levels than when given as a single intra-articular injection. Serum cortisol levels were substantially suppressed for up to 1 week, and this effect was seen at all dose levels.

It has been clear since the introduction of intra-articular steroid therapy that its effects are not confined to the joint injected. Steroid absorbed from the synovial cavity induces an improvement in indices of generalised joint inflammation.[1] This phenomenon has been shown to parallel a reduction in endogenous cortisol production, with evidence of suppression of the hypothalamic-pituitary-adrenal axis.[2 3] More recently the technique of thermography has been employed to demonstrate a beneficial effect on inflamed joints distant to the site of intra-articular steroid injection,[4] though the same investigators were in a more recent study unable to confirm statistically significant systemic improvement following injection.[5]

Until relatively recently only rather indirect evidence of steroid absorption from the joint has been available. The development of sensitive assays for estimation of commonly used synthetic steroids now permits detailed study of their absorption.[4 6]

Using a radioimmunoassay procedure for methylprednisolone we measured blood levels of this steroid following injection of various doses into one or both knee joints. In addition the effects on adrenal function as indicated by serum cortisol were also monitored.

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Patients and methods

Twenty-one inpatients with rheumatoid arthritis participated in the study. All had inflamed knees and all underwent bedrest for the duration of the study. According to their therapeutic requirements one or both knees were fully aspirated, the volume of synovial fluid was recorded, and the joint was injected with either 40 mg or 80 mg of methylprednisolone acetate (Depo-Medrone). As Table 1 shows, this resulted in 4 groups of patients. There was thus a wide range of injected steroid doses, from a minimum of 40 mg to a maximum of 160 mg. None of the patients had received either oral or intra-articular steroids for at least 2 months prior to the study. The intra-articular methylprednisolone injections were administered at 0800 h in each case. Blood samples were withdrawn immediately prior to

Table 1 *Administration of methylprednisolone acetate (Depo-Medrone)*

Group no.	*No. of patients*	*Mean age (years)*	*Joint(s) injected*	*Dose of methylprednisolone injected into each joint (mg)*
1	5	62	1 knee	40
2	6	59	2 knees	40
3	6	54	1 knee	80
4	4	59	2 knees	80

injection and then at intervals of 1,2,4,6,8,12, and 24 hours. Subsequent samples were taken daily for 7 days between 0800 and 1000 h. Serum was separated immediately and stored frozen until analysed. Levels of methylprednisolone and cortisol were estimated on each sample.

STEROID ANALYSES

Serum cortisol was measured by a fluorimetric method,[7] and serum methylprednisolone levels were estimated by a radioimmunoassay. Serum (0·5 ml) was extracted with 2 × 3 ml ethyl acetate, extracts were combined and evaporated to dryness at 40°C. The residue was reconstituted to 0·5 ml with 0·1 M phosphate buffer, pH 7·4 and 0·1 ml, in duplicate, was taken for radioimmunoassay. The sample or the standard (0·1 ml), after the addition of antiserum (0·1 ml, 1:3200 initial dilution) and ^{3}H-methylprednisolone (0·1 ml, 20 000 d.p.m.), was made up to 0·5 ml with phosphate buffer. The mixture was then incubated for 2 h at 4°C before the addition of 0·1 ml of a suspension of 0·5% Norit A charcoal and 0·05% Dextran T70 in buffer. The rest of the procedure and validation of the method were carried out as described previously for prednisolone.[8] The antibodies were found to bind equally well with methylprednisolone and its acetate derivative, the form in which the drug was administered. In comparison, the percentage cross-reactivity of the possible metabolites such as methylprednisone, 20-dihydromethylprednisolone, and 20-dihydromethylprednisone were 7·3, 11·4, and 4·3 respectively. All results are therefore referred to as total MP concentrations in serum and represent the sum of the concentration of methylprednisolone and related compounds mentioned above.

Results

The peak serum concentrations of total methylprednisolone (MP) and the times of the peaks are shown in Table 2. In most patients the serum drug levels reached their maxima at times between 4 and 8 h after the dose and the drug cleared from circulation almost completely, depending on the size of the dose, within 3–5 days. For example, 72 h after a 40 mg dose in one knee, MP was not detectable in serum of 2 out of 5 patients: in the rest it was present at levels below 29·4 nmol/l.

Despite the marked individual variation in the serum drug concentrations observed at all dose levels, raising the size of the dose invariably produced corresponding changes in serum peak MP levels and its bioavailability as reflected in the 'area under serum curve.' Doubling the 40 mg single injection would have, but for patient 3, produced a proportional rise in the mean serum peak MP level (Table 2). It appeared, however, that when 80 mg methylprednisolone was given as 40 mg into each knee there was considerably greater absorption than when the entire dose was injected into a single joint (Fig. 1). Similarly, the mean peak serum MP level rose from 213·6 to 1244 nmol/l when, instead of one knee, both were injected with 80 mg of the drug.

Table 2 *Serum methylprednisolone* after intra-articular injections*

Group no.	*Patient no.*	*Amount of steroid injected into each joint (mg)*	*Maximum serum conc. of methylpred. (MP) (nmol/l)*	*Mean maximum serum conc. (nmol/l)*	*Time of peak (h)*	*Mean area under curve (nmol/l/h)*
1	1	40	72·1	178·9	12	6275
	2	1 knee	109·5		4	
	3		475·3		4	
	4		114·8		2	
	5		122·8		2	
2	6	40	288·4	574	4	16 654
	7	2 knees	640·8		6	
	8		288·4		8	
	9		720·9		4	
	10		918·5		8	
	11		587·4		6	
3	12	80	192·3	213·6	6	7142
	13	1 knee	200·3		4	
	14		253·7		6	
	15		170·9		4	
	16		288·4			
	17		176			
4	18	80	1377	1244	8	30 974
	19	2 knees	424·6		4	
	20		2670		6	
	21		499·3		6	

*All MP values are expressed as methlprednisolone.

Table 3 *Serum cortisol levels after intra-articular methylprednisolone injections*

Steroid injection	*Mean resting cortisol (nmol/l)*	*Cortisol (nmol/l) at times after methylprednisolone dose*		
		24 h	*3 days*	**6/7 days*
Group 1; 40 mg, 1 knee	344·8 ± 33	113 ± 55	226 ± 88	287 ± 102
Group 2; 40 mg, each knee	405·5 ± 118	71·7 ± 16	129·9 ± 88	303 ± 110
Group 3; 80 mg, 1 knee	372·4 ± 96	146 ± 91	270 ± 102	358·6 ± 82
Group 4; 80 mg, each knee	408 ± 14	127 ± 47	115·8 ± 74	275·8 ± 126

*Samples from group 2 were collected 6 days after the injection, and the others were taken a day later.

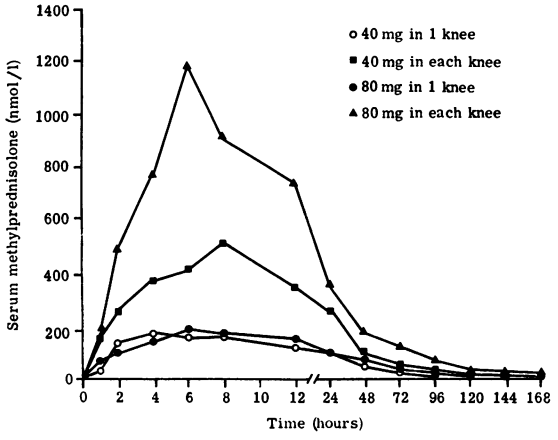

Fig. 1 *Mean serum methylprednisolone levels following intra-articular injections of methylprednisolone acetate.*

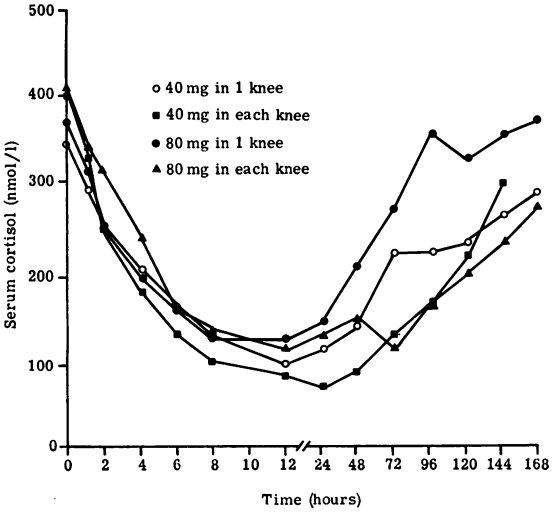

Fig. 2 *Mean serum cortisol levels following intra-articular injections of methylprednisolone acetate.*

Serum cortisol levels before and at various times after methylprednisolone are shown in Table 3. In all groups the adrenal function as indicated by serum cortisol was suppressed between 64–81% at 24 h after injection. This effect of a single dose still remained after 3 days (Fig. 2). With a few exceptions (cases 2, 11, and 19) serum cortisol was restored to values within the normal range after 1 week.

Discussion

Previous studies of the absorption of synthetic steroid following intra-articular injection have been carried out with various formulations of prednisolone.[4 6] Two important points have emerged from these investigations. Firstly, the steroid is absorbed from the joint at a slower rate than after a comparable oral dose.[6] Secondly, the rate of steroid absorption and the duration of local and systemic effect are related to the solubility of the preparations.[4] Less soluble formulations of prednisolone such as prednisolone tributylacetate are absorbed more slowly than the more soluble acetate compound, and the effects are more prolonged. Esselinckx *et al.*[4] reported that the peak plasma levels of injected steroid were seen at 24–48 hours, depending on solubility. However, their first plasma steroid estimation appears to have been at 24 hours after injection, and any difference between these values and drug levels at earlier times cannot be discerned from the data presented. Reeback *et al.*[6] demonstrated that peak plasma prednisolone levels were achieved at 2–4 hours after intra-articular injections of 50 mg or 100 mg of prednisolone acetate, results similar to those of Oka.[9] Our findings with methylprednisolone acetate are in accord with this work except that methylprednisolone acetate is absorbed from the knee joint cavity at a rate slower than that of prednisolone acetate.

We also confirmed the findings of others in that there was a complementary fall in serum cortisol levels and that this effect persisted for up to 7 days. However, neither the magnitude of this effect nor the amount of injected steroid remaining in circulation

at 7 days was related to the dose or the number of joints injected.

As might be expected, the quantity of steroid absorbed from the joint bears a close relationship to the amount injected. It was interesting that administering a given dose of steroid as 2 intra-articular injections resulted in greater absorption than when it was given into a single joint. We interpret this to imply that it is the total surface area of inflamed synovial membrane to which the steroid is exposed that determines the degree of absorption. We found no relationship between the volume of the joint effusion and subsequent steroid absorption, but this is a poor guide to the surface area of the joint lining, since variations in the degree of villous formation will ensure that the volume of the joint cavity and the surface area of its lining are widely disparate.

The degree of adrenal suppression, as reflected in depressed cortisol levels, did not vary significantly with the dose regimen and indicated that the minimum dose used in this study (i.e., 40 mg methylprednisolone) was sufficient to induce maximal suppression. Koehler *et al.*[3] showed that the adrenal response to insulin hypoglycaemia was markedly impaired 48 hours after intra-articular corticosteroid injection. The prolonged suppression of serum cortisol observed in the present study may have important clinical implications. The rheumatoid patient who either requires major surgery or develops a serious intercurrent illness soon after intra-articular steroid therapy may theoretically be at risk through being unable to mount an adequate physiological response to such stress. Although we are unaware of any reports of such an occurrence, the possibility of this happening despite the presence of synthetic glucocorticoids in circulation has to be borne in mind.

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