Plasma steroid levels after intra-articular injection of prednisolone acetate in patients with rheumatoid arthritis

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SUMMARY Eight patients with rheumatoid arthritis received an intra-articular injection of either 50 mg or 100 mg of prednisolone acetate into the knee joint. After the injection plasma levels of prednisolone were measured by radioimmunoassay and plasma cortisol levels were estimated fluorimetrically. Peak prednisolone levels were reached at between 2 and 4 hours after the intra-articular injection at both dosage levels, though the peak was higher with the larger dose. The 50 mg dose did not have any effect on the plasma cortisol level at 24 or 48 hours, but there was some suppression of plasma cortisol levels for up to 48 hours after the 100 mg dose.

The intra-articular use of steroids is now well established in the inflammatory arthropathies as an effective adjunct to other modes of treatment. The anti-inflammatory effect of the corticosteroid is believed to extend beyond the confines of the joint into which it has been injected, an effect which was noted early in the use of intra-articular steroid injection (Bywaters and Dixon, 1953). Systemic effects that have been observed include a fall in circulating eosinophils (Mason and Ward, 1953); suppression of plasma cortisol levels (Shuster and Williams, 1961); and suppression of the hypothalamic-pituitary axis (Koehler *et al.*, 1974). These effects would all follow the absorption of corticosteroid from the synovial cavity, a phenomenon which has been shown directly with cortisol and indirectly with prednisolone derivatives (Bain *et al.*, 1967).

Sensitive radioimmunoassay and competitive protein binding techniques are now available for the estimation of synthetic corticosteroids. One such procedure (English *et al.*, 1974) was used in the present study in an attempt to confirm the systemic absorption of prednisolone acetate injected into an inflamed joint and to gauge the blood levels achieved.

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Patients and methods

Eight patients, 4 males and 4 females, with rheumatoid arthritis participated in the study. They all had inflamed knee joints and were undergoing bed rest in hospital. One knee of each patient was aspirated as fully as possible and either 50 mg or 100 mg of prednisolone acetate injected into the joint between 9 am and 11 am. None of the patients had received steroids either orally or by intra-articular injection for at least 2 months prior to the study. The first blood sample for steroid assays was withdrawn immediately before the injection, and subsequent samples were collected at intervals up to 48 hours. The patients remained on bed rest throughout this time. The plasma was separated and stored frozen until analysed.

STEROID ANALYSES

The measurement of prednisolone in plasma was carried out by the method previously described (English *et al.*, 1974). The steroids were extracted from the plasma with acetone and separated by thin layer chromatography (silica gel HE 254 plates with CH₂Cl₂/MeOH/H₂O, 150/10/1 v/v as the solvent system). Prednisolone was then eluted and measured by the competitive binding system. Plasma fluorogenic 11-OH steroids, 'cortisol', were measured by a fluorimetric method (Mattingly, 1962).

Results

Peak plasma prednisolone levels observed after a single 50 mg injection are shown in Table 1. These levels ranged from 119 to 417 nmol/l (43 to 150 ng/ml) and were reached between 2 and 4 hours after administration of the prednisolone. Small amounts of prednisolone ranging from 33 to 157 nmol/l (12 to 56 ng/ml) were still detectable in the circulation of all patients after 24 hours. At 48 hours the amount of prednisolone remaining was too low to measure in 3 of the 6 patients and just detectable in the others. A 50 mg dose of prednisolone had no demonstrable effect on plasma cortisol levels at 24 hours or 48 hours after administration (Table 2).

After 100 mg of prednisolone 1 (no. 4) of the 3 patients studied had plasma prednisolone levels that were not markedly different from those observed in the same patient given a 50 mg dose. In the other 2 patients, who had not been previously studied, peak plasma prednisolone levels were higher but were reached within the same time interval as the lower dose (Table 3). Appreciable amounts of the drug were still present in the blood at 24 h and 48 h, and there was evidence of cortisol suppression in these cases even at 48 h (Table 2). No correlation was

Table 3 Plasma prednisolone concentrations (nmol/l) after a single 100 mg intra-articular injection of prednisolone acetate (nmol/l = ng/ml $\times$ 2.78)

Patient no.	30 min	1h	2h	4h	8h	24h	48h
4	138	199	342	144	113	50	22
7	110	552	453	455	458	229	119
8	593	654	777	814	649	290	210

observed between individual patients' weight, disease activity (as reflected by the erythrocyte sedimentation rate), or volume of fluid aspirated from the joint and either the peak plasma prednisolone levels or the time at which the peak levels were reached.

Discussion

The data presented here show that prednisolone is absorbed from the synovial cavity but at a slower rate than after a comparable oral dose (Table 4) (figures derived from normal volunteers who took oral prednisolone: English *et al.*, unpublished data). While in all cases plasma prednisolone levels reached a peak between 2 hours and 4 hours after the intra-articular injection, the peak concentration achieved varied with both the amount of steroid given and the individual patient. This is in agreement with the findings of Oka (1958), who measured plasma unconjugated 17-hydroxycorticosteroids by a modification of the Porter Silver reaction after the intra-articular injection of cortisol and cortisone. The difference between the levels reported in Oka's study and those presented here may be attributable in part to the use of a more specific and sensitive method of plasma steroid measurement in the present work as well as to differences in the nature of the steroid injected.

In contrast to the results presented here Esselinckx *et al.* (1976) have, in a preliminary communication, stated that plasma prednisolone concentrations did not reach their peak levels until 48 hours after intra-articular injection. These authors used 3 different derivatives of prednisolone—namely, the acetate, pivalate, and tributyl acetate—only one of which,

Table 1 Plasma prednisolone concentrations in nmol/l after a single 50 mg intra-articular injection of prednisolone acetate (nmol/l = ng/ml $\times$ 2.78)

Patient no.	30 min	1h	2h	4h	8h	24h	48h
1	—	+	282	196	127	80	+
2	80	—	—	119	99	33	28
3	—	52	204	376	312	157	30
4	138	190	403	237	190	63	+
5	+	86	345	323	240	30	28
6	80	177	362	417	395	47	+
Mean		126	319	278	227	68	29
S.E.		34	35	46	46	19	+

+ = Not measurable; sensitivity of the assay 15 nmol/l. — = Not sampled.

Table 2 Plasma cortisol levels (nmol/l) after a single intra-articular dose of prednisolone acetate (nmol/l = ng/ml $\times$ 2.75)

Patient no.	Dose of prednisolone	Morning cortisol level (nmol/l)		
		Basal value	24h after dose	48h after dose
1	50 mg	345	309	364
2	50 mg	284	193	229
3	50 mg	647	326	345
4	50 mg	734	497	834
5	50 mg	414	425	552
6	50 mg	386	353	375
4	100 mg	425	166	243
7	100 mg	450	232	293
8	100 mg	555	127	168

Table 4 Mean ($\pm$ SD) plasma prednisolone concentrations obtained in normal volunteers after a single oral dose of prednisolone (nmol/l = ng/ml $\times$ 2.78)

Dose (mg)	Peak concentration (nmol/l)	Time after dose (h)	No. of subjects
5	171 $\pm$ 39	2	5
10	287 $\pm$ 41	1	10
15	384 $\pm$ 33	1	6
30	828 $\pm$ 63	1	6

prednisolone acetate, was chemically identical with the material used by ourselves. Differences in formulation may account for the discrepancy between their observations and our own, but further comparison must await publication of a fuller report of their findings.

In the present study the administered steroid, at both dosage levels, had largely disappeared from the circulation by 48 h. After the smaller dose (50 mg) there was insufficient prednisolone remaining in the circulation to produce consistent suppression of plasma cortisol levels at 24 h after the intra-articular injection. After the larger (100 mg) dose, on the other hand, plasma cortisol levels were still suppressed after 48 hours. It is evident that measurement of plasma steroid levels following intra-articular injection of artificial steroid drugs and their effect on adrenocortical function warrant further attention.

The effect of the various recommended intra-articular dosage regimens on adrenal function cannot be fully predicted from the data presented here. It is likely that further investigation, especially of the newer synthetic corticosteroids, which are less water soluble than prednisolone acetate, and for which immunoassays now exist, will provide useful information on the difference between them, such as their therapeutic potency and duration of action.

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