The effect of intra-articular steroids on plasma salicylate concentrations

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1 Plasma salicylate concentrations and salicylate clearances were evaluated in 10 patients before and then 3 days after the intra-articular administration of glucocorticoid steroids. All patients were on chronic salicylate treatment, the dosage varying from 1.3–4.6 g day⁻¹ of enteric-coated aspirin.

2 The mean steady state plasma concentration ($\pm$ s.e. mean) of salicylate decreased significantly after intra-articular steroid (90.9 ± 14.8 mg l⁻¹ – 64.7 ± 8.9 , $P < 0.05$), whilst the mean clearance increased significantly (87.3 ± 20.6 ml min⁻¹ – 120.6 ± 28.3 , $P < 0.05$).

3 In these paired studies, the intra-articular administration of steroids lead to a significant decrease in plasma salicylate levels in patients taking enteric-coated aspirin.

Keywords glucocorticoid steroids intra-articular salicylate

Introduction

Salicylates continue to be widely used in the management of many rheumatic diseases. A number of studies have suggested that glucocorticoid steroids interfere with metabolism of salicylates resulting in a lowering of plasma concentrations during concurrent administration of steroids (Klinenberg & Miller, 1965; Graham *et al.*, 1977; Bardare *et al.*, 1978). These studies, however, have only considered small numbers of patients taking oral steroids and have been cross-sectional in nature. Whether a similar change is associated with intra-articular steroids is not known. The present study has been designed to investigate longitudinally and prospectively the effects of the administration of intra-articular steroids on salicylate levels in patients who were receiving chronic multiple dosing with salicylate.

Methods

Subjects

The subjects were 10 patients of the Rheumatic Disease Unit who were admitted to hospital for the administration of intra-articular steroid. Their clinical details are shown in Table 1. There were three males and seven females, the age range being from 30–78 years. All were receiving enteric-coated aspirin (Ecotrin, Smith Kline and French Laboratories (Aust), or Rhusal, GP Laboratories), the total daily dose varying from 1.3 to 4.6 g. The dose of enteric-coated aspirin for the duration of the study had been that for more than 4 weeks prior to the pre-treatment study.

All concurrent medications (Table 1) were continued throughout the study, administered at the same time of day on each occasion, and no

Table 1 Patient information

Patient Sex	Diagnosis*	Age (years)	Weight (kg)	Plasma albumin (g l ⁻¹)	Aspirin (Ecotrin: Rhusal) (g day ⁻¹)	Other medications (total/day)
A Female	O.A.	71	78	41	3.9	nil
B Female	R.A.	78	65	36	1.3	Naproxen 500 mg; Sulindac 400 mg, Gold 50 mg week ⁻¹ (intramuscular).
C Female	R.A.	58	57	41	3.25	Sulphasalazine 2 g; Indomethacin 100 mg; Ibuprofen 1600 mg; Thyroxine 100 µg; Prednisolone 10 mg <i>alt die</i> .
D Female	R.A.	76	55	42	1.95	Ibuprofen 1.2 g; Sulindac 400 mg; Thyroxine 50 µg; Prednisolone 15 mg <i>alt die</i> .
E Female	R.A.	57	67	37	4.55	Indomethacin 75 mg; d-Penicillamine 1.2 g; Throxine 100 µg.
F Female	R.A.	36	55	38	2.6	Indomethacin 150 mg; Naproxen 1 g.
G Female	R.A.	30	53	40	3.9	Sulphasalazine 2 g; Naproxen 1 g; Insulin.
H Male	R.A.	46	77	39	3.9	Cyclophosphamide 100 mg; Naproxen 1 g.
J Male	P.A.	42	61	34	3.9	Indomethacin 200 mg.
K Male	R.A.	64	66	41	1.95	Naproxen 750 mg; Gold 50 mg week ⁻¹ (intramuscular). Allopurinol 300 mg; Prednisolone 25 mg <i>alt die</i> .

* O.A., Osteoarthritis; P.A., Psoriatic arthritis; R.A., Rheumatoid arthritis.

additional agents were introduced during the study.

Study design

All patients remained in hospital longer than the duration of this study. Rheumatology Unit policy dictates that following intra-articular administration of steroid the injected joint(s) or tendon sheath be immobilized for at least 3 days, where possible with non-flexible splinting (e.g. for a knee, Richard's splint, a shoulder spica-type bandaging) and enforced rest. This meant that the majority of patients were on strict bed-rest for the full 4 days including pretreatment. The majority of patients had active rheumatoid disease at the time of the study with multiple joint involvement.

Plasma salicylate concentrations were measured in samples collected by venepuncture over 8 h according to the following schedule, 0, 1, 2, 3, 4, 6 and 8 h where $t = 0$ was the time of the first sample and in most of the patients close to their morning dose of aspirin (Table 2). Plasma salicylate concentrations were measured on two occasions, before receiving intra-articular steroids (pre-steroid dose) and again 3 days after (post-steroid dose). The timing of the pre-

steroid and post-steroid studies was carried out as closely as allowed by the other demands of patient care. In one patient (A) both studies were carried out in the afternoon. The time of dosing is shown in Table 2, as are additional routine doses of aspirin given during the course of both studies, later in the day. Table 2 also shows the dose of intra-articular steroid, and the joint or joints injected.

Assay methods

Heparinized samples were stood at 4°C until the end of the study, at which time the plasma was separated, and then frozen until analysed in batches.

Plasma salicylate was estimated using the high pressure liquid chromatographic (h.p.l.c.) system described below.

To 1 ml of acetonitrile in a pointed tube was added, whilst vortexing, 100 µl of sample. The mixture was centrifuged and 500 µl of the supernatant transferred to a round bottomed tube and taken to dryness in a water bath at 45°C. The residue was dissolved in 100 µl of 35% acetonitrile in 0.03% phosphoric acid and an aliquot injected onto a Waters Assoc. h.p.l.c. equipped with a Waters 450 variable-wavelength UV detector operated at 320 nm, at a sensitivity of $\times 0.02$ a.u.s. The column (30 cm $\times$ 4 mm) was

Table 2 Study data relating to dosing and dosage

Patient	Study dose (s) of aspirin (mg)	Dosage time (s)	Time study commenced	Total intra- articular steroid (mg)*	Sites†
A	1950	0800 2000	1300	M.80	One knee
B	650	0800	0800	M.160	Both knees
C	1300 650	0800 1200	0900	M.160	Knee Both elbows
D	650 650	0800 1200	1000	M.40	Shoulder
E	1300 1300	0800 1200	0815	T.10 D.4	Wrist Median nerve
F	1300	0800	0800	M.160	Both knees
G	1950	0800	0815	M.80	Both knees
H	1300 1300	0800 1200	0910	M.80	Both knees
J	1300 1300	0800 1200	0800	T.15	Wrist, P.I.P.
K	650	0800 1200	0820	D.8	Two tendons

* D: Dexamethasone (Decadron) 4 mg ml⁻¹; M: Methylprednisolone (Depromedrol) 40 mg ml⁻¹; T: Triamcinolone (Kenacort) 10 mg ml⁻¹.

† PIP: Proximal interphalangeal joint.

packed with μ Bondapack C_{18} (Waters Assoc. Milford, Mass., U.S.A.). Samples were introduced by means of a variable-loop injector (Waters Model U6K). The eluent was 35% acetonitrile in 0.03% phosphoric acid used at a flow-rate of 2.0 ml min^{-1} . A linear correlation of peak height to concentration was obtained between 25 and 200 mg l^{-1} . Absolute recoveries over this range were $96.6 \pm 2.5\%$ ($n = 10$). The assays were performed using external standards of 250 and 500 ng of salicylate injected onto the column in similar solvent. (Coefficients of variation at 25 and 200 mg l^{-1} were 1.0% ($n = 5$) and 1.7% ($n = 5$) respectively.

Calculation of pharmacokinetic parameters

The average steady state serum concentrations of salicylate ($\bar{C}_{ss}$) were calculated using the following equation:

$$\bar{C}_{ss}(\text{SA}) = \frac{t_2 \int_{t_1} C \cdot dt}{t_2 - t_1}$$

where $\bar{C}_{ss}(\text{SA})$ is the steady state serum salicylate concentration expressed in mg l^{-1} :

$$t_2 \int_{t_1} C \cdot dt$$

is the area under the serum salicylate concentration-time curve from time t_1 to t_2 in $\text{mg ml}^{-1} \text{ h}$ (calculated by the trapezoidal rule), and $t_2 - t_1$ is the duration of the dosing interval in hours (Wagner *et al.*, 1965). Clearance (CL) was calculated by the equation:

$$\text{CL} = F \cdot \frac{\text{Dose/dose interval}}{\bar{C}_{ss}}$$

where F = systemic absorption.

The assumption made was that F was equal to 1, (that is, that absorption was complete) and that absorption did not change over the duration of the study, being the same both pre- and post-steroid treatment. If absorption was not complete, but F remained constant for pre- and post-steroid calculations then the calculated values for clearance would still be valid, but show relative change only. For purposes of comparison, it was considered that within any individual patient in hospital 4 days, taking the same manufactured preparation, bioavailability should be relatively consistent.

Statistics

Data were compared using paired Student's t -tests.

Results

Table 3 shows the results before and after the administration of steroids of the plasma salicylate concentrations over the 8 h period in all patients. Before steroids, only one (A) of the patients had plasma salicylate concentrations which are generally considered to be therapeutic, i.e., greater than 150 mg l^{-1} (Hart, 1980). She was the only patient not taking additional non-steroidal analgesics (NSAID). During the course of the study the fluctuations in the plasma concentrations in three of the patients are related to the ingestion of a second dose of aspirin (Table 2). The other four patients who took aspirin during the study did not show any apparent effect, presumably due to very delayed absorption in the small intestine. The variability in absorption between patients is marked comparing the large increase in D with that in E for instance. The pattern of apparent absorption of salicylate is similar in individual patients in each of the two studies. However, neither the total daily dose of aspirin, nor the study doses were related to either the plasma concentrations *per se* (Table 3) or the data transformed into average plasma concentrations (Table 4). The three patients taking alternate day oral prednisolone tended to have lower plasma concentrations.

Three days after intra-articular steroids the average steady state plasma concentration fell in eight of the 10 subjects. This was independent of the steroid used, occurring in six out of the seven receiving methylprednisolone, and two of the three receiving triamcinolone and/or dexamethasone. The two patients who showed the reverse, i.e. an increase in plasma concentration, received steroid doses which tended to be slightly lower (40 mg methylprednisolone (D) and triamcinolone 10/dexamethasone 4, (equivalent to 30 mg methylprednisolone) (E)). The former patient was also on oral prednisolone second daily. The site of administration did not appear to influence the effect; neither was it related to aspirin dose nor plasma salicylate concentration, nor total daily dose of NSAID. The overall group showed a significant decrease in steady state plasma concentration, with a concurrent increase in calculated clearance.

Discussion

It has been previously suggested that glucocorticoid steroids result in lowering of plasma salicylate concentrations. However, most studies have been carried out comparing different patient groups according to whether or not they

Table 3 Plasma salicylate concentrations (mg l⁻¹)

Patient	Time (h) after salicylate dose						
	0	1	2	3	4	6	8
<i>Before intra-articular steroid</i>							
A	237	197	191	198	200	196*	193
B	82		65	83		89	106
C	97		76	62*	56	47	49
D	27		30*	121	104	96	
E	97	79	85	82	74*	88	78
F	188		136	109	79	60	121
G	130			107	107	89	96
H	53	46	41	*	32	25	27
J	94		117	100	91*	125	106
K	91		84	71	57*	56	57
Mean	110		92	104	89	87	93
± s.e. mean	20.6		17.6	14.2	17.0	15.9	17.2
<i>After intra-articular steroid</i>							
A	141	114	123	106	100	91*	78
B	36		33	42		43	44
C	60		49	43*	47	39	38
D	36		79*			108	87
E	132		104	90	87*	76	68
F	140		91	75		48	86
G	74			67	57	75	75
H	24	23	26	23*	21	29	45
J	13		47	88	68*	127	103
K	37		32	31	28*	33	28
Mean	69		65	63	58	67	65
± s.e. mean	16.7		12.4	10.3	11.9	11.3	8.3

* Indicates the ingestion of a second dose of aspirin as indicated in Table 2.

Table 4 Calculated average plasma steady state concentrations* and clearances† before and after intra-articular steroid

Patient	Average $\bar{C}_{ss}$ (SA)* (mg l ⁻¹)		Clearance† (ml min ⁻¹)	
	Before	After	Before	After
A	198	103	27	52
B	84	40	21	45
C	63	45	107	150
D	59	85	63	44
E	82	91	116	104
F	108	78	75	104
G	105	69	52	79
H	34	27	238	300
J	108	78	69	96
K	68	31	106	232
Mean ± s.e. mean	91 ± 14.9‡	65 ± 8.9‡	87 ± 20.6§	121 ± 28.3§

$$* \text{ Average } \bar{C}_{ss} = \frac{t_2}{t_1} \int \frac{C \cdot dt}{t_2 - t_1}$$

$$† \text{ Clearance (CL)} = F \cdot \frac{\text{dose/dose interval}}{\bar{C}_{ss}}$$

where F is the systemic availability, which is assumed to be the same on the two test days, and to equal 1.

‡,§ Significantly different, $P < 0.05$ using paired t -test.

were receiving concurrent steroids (Graham *et al.*, 1977; Bardare *et al.*, 1978). This present study has been designed to investigate the effect of short-term use of steroids on the plasma salicylate concentrations in individual patients. The use of intra-articular steroids is not uncommon in the management of arthritis within individual joints, and offers a simple model for investigating the initial effects of steroids on plasma salicylate levels when the salicylate is being taken chronically. Intra-articular steroids are well absorbed from the joint into the systemic circulation with significant plasma levels being attained (Bertouch *et al.*, 1983).

The present study shows that the administration of intra-articular steroids causes significant falls in the steady state plasma salicylate concentrations as estimated before the administration of steroid and 3 days after. The clearance of salicylate was significantly increased in parallel with this decrease in plasma concentration. Whilst the greatest change in the current studies occurred in the patient who had the highest salicylate level, and was not receiving any other anti-inflammatory agents, the response was not apparently related to salicylate dose, nor glucocorticoid used, although there is a suggestion of a threshold for the steroid. The increase in clearance agrees with the results of Graham *et al.* (1977), who showed that the long-term oral administration of steroids was associated with higher clearances of salicylate and confirmed in the study in the three patients on alternate day maintenance. In their cross-sectional study, the number of patients receiving intra-articular injections was small, and they were unable to identify any effect on salicylate plasma levels. However, there was no statement as to the timing of the studies in relationship to intra-articular administration. It is also of interest that the changes were seen in two of the three patients who were receiving alternate day maintenance steroids (Table 3; C, K). In both patients, the first and second profiles were on the same day as their oral steroids, i.e., possibly additive. Alternate day steroids have been promoted as being less disturbing physiologically, particularly to the hypothalamic-pituitary-adrenal axis (Melby, 1977).

These data are concerned with short-term administration of steroids and their influence on steady state salicylate levels in chronic dosing. The mechanism may not be the same as that seen with chronic steroid dosing, although net outcome, namely increased clearance is similar. This current study allows only speculation concerning mechanism(s) of action. The early case (Klinenberg & Miller, 1965) identifying the

interaction between salicylates and steroids described the appearance of salicylate toxicity accompanying withdrawal of oral steroids. This is in keeping with the current data. The authors of that report ascribed the changes to an increased turnover of salicylate, short term (3 day) administration of hydrocortisone resulting in an increase in glomerular filtration rate, with a consequent clearance of free, unbound salicylate. However, there were wide variations in response. Alternative, or additional explanations, (for it may well be multifactorial), may be an increased rate of catabolism of salicylate, possibly secondary to enzyme induction by steroid. This would be accompanied by an increase in, and/or change in the pattern of urinary salicylate metabolites, the former being described in patients on chronic steroid therapy (Graham *et al.*, 1977). In the current short term study, whilst such induction would be rapid, it is consistent with the temporal sequence of glucocorticoid-receptor interaction and resulting protein synthesis (Melby, 1977). Alternatively, steroids are proposed also to cause wide amplification of biological effects (Granner, 1979) over and above their direct receptor dependent functions above. This may be the explanation for the increased clearance of antipyrine in the presence of infused hydrocortisone which was demonstrated by Breckenridge *et al.* (1973), but not confirmed by Flanagan & Richens (1974). With both enzyme induction or a permissive effect of steroids, differing glucocorticoids may be expected to give qualitatively similar results, quantitatively different according to potency. A further possibility to be explored is that the free salicylate concentration may be increased by administration of steroid, with resultant increased clearance and a net decrease in the total plasma salicylate concentration. The mechanism(s) via which such displacement may occur are complex (Fehske *et al.*, 1981) and could be via direct competition for binding sites on albumin (Potter & Offerman, unpublished observations), unlikely due to the varying steroids and doses used, and/or via changes in tertiary conformation of the albumin molecule, induced by non-esterified fatty acids (NEFA), there being a complex interaction between salicylate and long-chain NEFA (Dawkins *et al.*, 1970). Glucocorticoids are permissive for the release of NEFA, which occurs as a consequence of the secretion of other metabolic hormones in response to stress (Beisel, 1975).

The current data do not allow any prediction concerning duration of effect. However, plasma cortisol concentrations remain suppressed for up to a week following intra-articular steroid

(Armstrong *et al.*, 1981), and if the mechanism involved enzyme induction, for instance, duration will be dependent upon the half-life of the protein or proteins involved.

The patients within this current study were selected using as the only two criteria that they were to receive intra-articular injections of steroid and were on chronic therapy of enteric aspirin. The doses varied widely (Table 1), and it is of interest that prior to steroid administration only one patient attained the currently-used therapeutic range consistently over 8 h. This suggests that in fact many patients who are receiving enteric-coated aspirin are probably on doses with plasma levels less than that considered to be optimal and further begs the question as to whether plasma salicylate concentrations should be monitored in more patients prior to the administration of further anti-inflammatory compounds. In view of the wide fluctuations seen in

the plasma concentrations in some of these patients, it also raises the question as to the most appropriate timing of such measurements in individual people, most appropriately being a trough level.

Does the lowering of plasma salicylate concentrations after intra-articular steroids pose a clinical problem? Although this aspect was not formally studied, it was the impression that patients did not have a flare in systemic disease activity because of the decreased salicylate concentration. The reason may lie in part in the systemic effects of the absorbed steroids, such that a clinical improvement in other joints, not those directly injected, is often observed (Bird *et al.*, 1979).

This work was supported by The Western Australian Arthritis and Rheumatism Foundation in a research grant to J. Edelman.

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(Received 17 June 1985,
accepted 5 October 1985)