Interaction of salicylate and corticosteroids in man

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Corticosteroids have been reported to decrease the plasma concentrations of salicylate when salicylates have been administered chronically at high doses. In the present study, two single, oral doses of sodium salicylate, 10 mg kg⁻¹ were administered to six adult subjects with a variety of inflammatory conditions both before and during treatment with daily oral doses of prednisone (12–60 mg). Concomitant prednisone therapy did not increase the whole body clearance of single doses of salicylate in these subjects (0.0275 ± 0.08 l kg⁻¹ h⁻¹ before prednisone; 0.0247 ± 0.03 l kg⁻¹ h⁻¹ during prednisone therapy; $P > 0.05$). These results indicate that corticosteroids do not alter the clearance of single doses of salicylate in man.

Keywords corticosteroids salicylate drug interaction clearance

Introduction

The concurrent use of glucocorticosteroids and salicylates is not uncommon in the treatment of rheumatic diseases. There are several studies which indicate that treatment with corticosteroids induces the metabolism of salicylate. Salicylate concentrations in plasma increased markedly when corticosteroid dosage was tapered in patients with rheumatoid arthritis (Klinenberg & Miller, 1965; Muirden & Barraclough, 1976) and, correspondingly decreased when prednisone was commenced (Koren *et al.*, 1987). In addition, it was noted that salicylate concentrations were substantially lower when corticosteroids were taken concurrently (Graham *et al.*, 1977; Bardare *et al.*, 1978) while, in a recent communication, it was reported that even intra-articular corticosteroids decreased the plasma concentrations of salicylate during chronic salicylate therapy (Edelman *et al.*, 1986). Klinenberg & Miller (1965) reported that corticosteroids enhanced the renal clearance of salicylate in some patients but their assay method was non-specific and salicylate could not be distinguished from its major urinary metabolite, salicylurate, which is

found in high concentration in the urine (Levy *et al.*, 1972). Consequently, it was considered to be more likely that corticosteroids induce the metabolism of salicylate (Graham *et al.*, 1977; Edelman *et al.*, 1986). By contrast to these results in patients, steady-state salicylate concentrations in plasma ($100\text{--}200$ µg ml⁻¹) were not lowered in dogs after prednisone 10 mg day⁻¹ had been administered orally for 6 days (Day *et al.*, 1976). The study described in this communication was designed to examine the interaction between corticosteroids and salicylate more closely in a prospective, cross-over trial of the effect of chronic corticosteroid treatment on the clearance of orally administered single doses of salicylate in humans.

Methods

Patients suffering from various inflammatory diseases, requiring treatment with corticosteroids, were recruited (Table 1) after they had given consent to participate in the study. The

Table 1 Patient characteristics and medications

Patient	Age (years)	Sex	Weight (kg)	Disease	Concurrent medications	Prednisone dose (mg day ⁻¹)
1	65	M	86	PMR*	nil	25
2	77	F	56	PMR	nitrazepam	20
3	76	M	67	PMR	nil	12
4	68	M	79	PMR	chlorthalidone aluminium hydroxide magnesium hydroxide	15
5	64	M	66	Tinnitus	cimetidine	60
6	31	M	71	Uveitis	nil	37.5–50

* Polymyalgia rheumatica.

study was approved by the Ethics and Research Committee of St Vincent's Hospital, Sydney. After fasting for 8 h, patients were given sodium salicylate (10 mg kg⁻¹) in aqueous solution (200 ml). When possible, medications were ceased at least 5 days prior to the study. Thus, subject 1 ceased prazosin, chlorthalidone and hydrochlorothiazide with amiloride, subject 2 ceased naproxen, subject 3 ceased indomethacin, paracetamol, methdilazine hydrochloride and promethazine hydrochloride and subject 5 ceased amitriptyline, lorazepam and calcium salts. Subject 3 took his last dose of indomethacin 20 h before the first single dose of salicylate. Some subjects continued various drugs throughout the study (Table 1), but these were not taken for at least 12 h before single doses of salicylate. Blood (10 ml) was collected from a forearm vein using an indwelling catheter, whose patency was maintained with heparin saline solution (10 units ml⁻¹). Sampling times were 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h following ingestion of the sodium salicylate. Lunch was allowed 4 h after the single dose had been administered. This single dose study was repeated after at least 3 weeks of treatment with prednisone (12–60 mg day⁻¹; Table 1). Four patients were given ammonium chloride 2 g every 6 h for 24 h prior to each single dose salicylate study, in order to acidify the urine and thus minimize excretion of unchanged salicylate (Day *et al.*, 1983, 1988). Urinary pH was monitored during the 12 h of the single dose study, all voids being tested for pH.

Plasma concentrations of salicylate were measured by the method of Rowland & Reigelman (1967). The whole body clearance of salicylate was determined by dividing the dose of drug administered by the area under the time course of salicylate concentrations in plasma between 0 and infinite hours (AUC). Because of its saturable metabolism, the clearance of salicylate is not constant and the calculated clearances presented in this paper are therefore only

apparent values, but are calculated in order to detect any changes in the rate of elimination of the drug. The AUC was computed using the trapezoidal rule. The AUC, from the last salicylate concentration to infinity, was estimated by dividing the last salicylate concentration by *k*, the apparent elimination rate constant. The half-life was estimated from the linear portion of the elimination phase of the semi-logarithmic plots of salicylate concentration vs time for each individual. It was assumed that the absorption of the dose was complete. The statistical significance of differences between treatment groups was determined, using Student's paired *t*-test.

Results

Neither the clearance of salicylate nor the apparent half-life of elimination changed significantly after 3 weeks corticosteroid treatment in the six patients (Table 2). The clearance changed by 10% or less in five of these six patients. In only one subject (subject 6) did the clearance increase. Subjects 3 and 5, who were not given any ammonium chloride during the study, because the solute load was considered to be medically contraindicated, did not show any increase in urinary pH or clearance of salicylate during dosage with prednisone (Table 2).

Discussion

This study failed to demonstrate any increase in the clearance of salicylate in six patients following the introduction of chronic corticosteroid therapy. This result is similar to that of a prospective study of this combination performed in dogs (Day *et al.*, 1976). It is not, however, in keeping with previous cross-sectional studies in which patients were taking large doses of salicylates chronically.

Table 2 Whole body clearances of salicylate ($l\ kg^{-1}\ h^{-1}$), half-lives of elimination (h) and mean $\pm$ s.d. ($n =$ at least 6 and up to 15 for each individual) urinary pH before and during treatment with prednisone

Subject	Before treatment			During treatment		
	Clearance ($l\ kg^{-1}\ h^{-1}$)	Half-life (h)	Mean pH	Clearance ($l\ kg^{-1}\ h^{-1}$)	Half-life (h)	Mean pH
1	0.0251	2.8	5.7 ± 0.6	0.0231	2.7	6.0 ± 0.0
2	0.0365	1.9	5.0 ± 0.0	0.0328	1.9	†
3*	0.0379	1.8	5.9 ± 0.2	0.0266	2.2	5.3 ± 0.3
4	0.0228	4.0	5.0 ± 0.0	0.0228	3.6	6.0 ± 0.0
5*	0.0191	2.8	7.0 ± 0.0	0.0175	2.5	5.2 ± 0.4
6	0.0238	2.0	5.0 ± 0.8	0.0253	2.3	6.0 ± 1.2
Mean	0.0275	2.6	5.6	0.0247**	2.5**	5.7**
s.d.	0.008	0.8	0.8	0.003	0.5	0.4

* No ammonium chloride administered.

† Not tested.

** $P > 0.05$; before prednisone vs during prednisone treatment.

The design of this interaction study was very much dependent upon the therapeutic needs of the patients involved. A randomized order of treatment with prednisone would have been preferable in this study but this was not possible in the patients studied since they started prednisone for therapeutic purposes. It would also have been better if all patients had received ammonium chloride but in two subjects this was contraindicated because the additional solute load may have precipitated cardiac failure. One patient was taking cimetidine, a drug known to inhibit some oxidative pathways of drug metabolism. However, oxidation is a minor pathway of the metabolism of salicylate and, furthermore, the dosage of cimetidine was constant. Consequently, it is reasonable to present the pharmacokinetic data on this patient.

Patient numbers are not large in this study. However, given a significance level of 0.05 and a β value of 0.8, this study with six subjects should have been able to detect at least a 20% increase in the clearance of salicylate induced by corticosteroids (Dobson, 1984). An increase in salicylate clearance of the order of 25–59% was anticipated from data reported in previous studies (Graham *et al.*, 1977; Klinenberg & Miller, 1965; Koren *et al.*, 1987; Edelman *et al.*, 1986). However, since most of the subjects had decreases in clearance of 10% or less, it would seem most unlikely that increasing patient numbers would unmask a substantial and significant increase in salicylate clearance.

One interpretation of the previous and present studies is that corticosteroids may only affect the clearance of salicylate in humans during high

dose, chronic treatment with salicylates. Chronic salicylate therapy is associated with an increase in the maximal rate of conversion of salicylate to salicylurate (Furst *et al.*, 1977; Day *et al.*, 1983, 1988), the major metabolic pathway of salicylate. This induction process could be enhanced in the presence of exogenous corticosteroids. An alternative hypothesis for the conflicting data is that corticosteroids may affect minor pathways of elimination of salicylate. During chronic high dose therapy with salicylate, the major metabolic pathway, which produces salicylurate, is near saturation (Levy, 1965; Levy *et al.*, 1972). Consequently, minor pathways become more significant with increasing doses of salicylate and, therefore, enhancement of any of these minor pathways by corticosteroid therapy would be more evident at high dosage rates of salicylate. One minor pathway of elimination of salicylate is the renal clearance of unmetabolized drug. This route of elimination is sensitive to changes in urinary pH and steady-state concentrations have been observed to fall markedly with small increases in urinary pH (Levy & Leonards, 1971; Hansten & Hayton, 1980). In the current study, urinary pH was controlled by the administration of ammonium chloride in four subjects, but in the two subjects who could not take ammonium chloride, neither urinary pH nor the clearance of salicylate increased. Urinary pH actually decreased in these two subjects. This result is consistent with the previous report of Graham *et al.* (1977) who found that oral corticosteroids did not increase urinary pH or the proportion of free salicylate excreted in urine.

This study was unable to show that moderate doses of prednisone given for at least 3 weeks had any affect upon the clearance of a single dose of salicylate. Further study of this interaction is of some importance but attention should be directed to an analysis of the pharmacokinetics

of salicylate in subjects taking chronic, high doses of salicylates.

The authors are indebted to the volunteers, Sister A. Borthwick for managing the clinical aspects of the study and Dr G. Major for referring a subject for study.

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(Received 8 April 1987,
accepted 20 May 1988)