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Pharmacokinetics of intravenous and oral salbutamol and its sulphate conjugate

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1 The pharmacokinetics of salbutamol and its sulphate conjugate metabolite were investigated after intravenous and steady-state oral administration of salbutamol to 10 healthy volunteers.

2 With intravenous administration, total plasma clearance was 480 ± 123 ml min^{-1}, elimination half-life was 3.86 ± 0.83 h and apparent volume of distribution was 156 ± 38 l. Urinary excretion of unchanged drug and sulphate conjugate were 64.2 ± 7.1% and 12.0 ± 3.1% of the dose, respectively.

3 With oral administration, systemic availability was 0.50 ± 0.04, and urinary excretion of unchanged drug and sulphate conjugate were 31.8 ± 1.9% and 48.2 ± 7.3% of the dose, respectively. The drug eliminated on the first-pass could be accounted for entirely as sulphate conjugate formed, presumably, in the intestinal wall.

4 Renal clearance of salbutamol was 291 ± 70 ml min^{-1} after intravenous and 272 ± 38 ml min^{-1} after oral administration, while the renal clearance of the sulphate conjugate was 98.5 ± 23.5 ml min^{-1} after oral administration.

5 Heart rate increased with increasing plasma salbutamol concentration, although a lag was evident. The effect on heart rate was lower after 24 h continuous oral salbutamol administration.

Keywords salbutamol pharmacokinetics

Introduction

Salbutamol (albuterol) is a potent β_2-adrenoceptor stimulant used widely for the treatment of bronchial asthma and in obstetrics for the prevention of premature labour (Avery, 1980). In spite of the widespread use of the drug there are few detailed pharmacokinetic data available, primarily because the plasma salbutamol concentrations resulting from normal doses are low.

To investigate the pharmacokinetics of salbutamol administered intravenously and orally we used a sensitive but convenient high pressure liquid chromatographic method with fluorescence detection (Hutchings *et al.*, 1983). To enhance detection of salbutamol in plasma, the drug was administered as a 2 h infusion in the intravenous study and the oral study was conducted during a dosage interval at steady-state.

Methods

Ten healthy subjects (five male and five female) aged 22 to 25 years (mean 22.9 years) weighing 52 to 80 kg (mean 62.2 kg) who were taking no

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other drugs participated in the study. The study, which was approved by the Hospital Ethics Committee, consisted of two phases, an intravenous phase and an oral phase. In both phases subjects fasted overnight prior to drug administration and no food or water was ingested for 3 h after the dose. Four of the subjects participated in the oral phase of the study first (subjects 3, 4, 7 and 8) while the other 6 subjects participated in the intravenous phase first. The phases were separated by at least 1 week.

For the intravenous phase, a loading dose of 400 μg salbutamol (as the sulphate salt) in 20 ml isotonic saline was administered by hand over 5 min via a peripheral vein in the arm. This was followed immediately by a constant infusion of salbutamol up to 2 h at a rate of 10 μg min^{-1} in normal saline (10 μg ml^{-1}) using a calibrated syringe pump (Vickers IP3).

In the first two subjects studied, the loading and maintenance doses were 200 μg and 5 μg min^{-1}, respectively. As plasma salbutamol concentrations in these first two subjects were lower than anticipated the doses were doubled for the remaining eight subjects. Venous blood was taken from an indwelling cannula at 0, 15, 30, 45, 60, 80 and 100 min and 2, 3, 4, 6, and 8 h after the commencement of the loading dose. A blank urine specimen was collected prior to dosing, then all urine was collected for the next 48 h. Heart rate and blood pressure were recorded (Hewlett Packard Twin Channel Monitor, Model 78332A) at the time of collection of each blood sample. Subjects remained supine during the infusion and then resumed normal activities.

For the oral phase, on the day prior to the study, each subject ingested one salbutamol 4 mg tablet (Ventolin, Glaxo) at 08.00, 16.00 and 24.00 h. At 08.00 h on the study day each subject ingested another 4 mg salbutamol tablet with 100 ml tap water. Venous blood was taken from an indwelling cannula at 0, 15, 30, 45, 60 and 90 min and 2, 3, 4, 6 and 8 h after dosing. Subjects emptied their bladder just before taking the tablet and all urine was collected for 8 h after the dose. Heart rate and blood pressure were recorded at the time of collection of each blood sample. Subjects remained seated for 2 h and then resumed normal activities. The concentration of creatinine was determined by auto analyzer (Jaffe reaction) in the 4 h plasma sample and in an aliquot of the pooled 0–8 h urine, for determination of creatinine clearance.

Plasma was separated from erythrocytes within 15 min of collection. In the intravenous phase of the study an aliquot of whole blood from one sample per subject was retained for the determination of the blood/plasma concentration ratio of salbutamol. Plasma, blood and urine were stored at −20° C until assayed.

In a separate study, the plasma protein binding of salbutamol was investigated by ultrafiltration (Micropartition System MPS-1, Amicon Corp. U.S.A.) using methods developed previously in our laboratory (Crankshaw *et al.*, 1985). Salbutamol did not adsorb significantly to the YMT membrane used. Binding was measured in quadruplicate in an aliquot of pooled blood bank plasma spiked to a salbutamol concentration of 50 ng ml^{-1} and in plasma from three volunteers spiked to 200 ng ml^{-1}.

Salbutamol in plasma ultrafiltrates and whole blood was assayed by the high pressure liquid chromatographic method of Hutchings *et al.* (1983), which uses fluorescence detection (excitation 230 nm, emission 309 nm, detection limit 1 ng ml^{-1}). For the assay of salbutamol in urine, the excitation and emission wavelengths were changed to 276 and 604 nm, respectively. This was because interfering peaks were present in the chromatogram when 230 nm/309 nm were used and because a lower sensitivity could be tolerated due to the relatively high concentrations of salbutamol in urine. At a salbutamol concentration of 1 μg ml^{-1} in urine the coefficient of variation was 2.5% ($n = 7$) and the detection limit was approximately 50 ng ml^{-1}.

Salbutamol sulphate conjugate in plasma and urine was assayed using a method developed in this laboratory (Hutchings, Morgan & Paull, to be published). The method is based on the assay of 4^1-hydroxypropranolol sulphate conjugate (Wingstrand & Walle, 1984). Briefly, to plasma or urine (1 ml) were added sodium hydroxide (0.1 ml, 2 M), tetrabutylammonium-hydrogen sulphate (0.5 ml, 0.1 M) and chloroform (5 ml). The mixture was vortexed and centrifuged, and the chloroform phase was separated and extracted with HCl (3 ml, 0.5 M). The acid phase was hydrolyzed by heating at 100° C for 20 min and an aliquot (200 μl) was then injected into the high pressure liquid chromatograph and assayed for salbutamol using the conditions described above for plasma or urine, as appropriate. Authentic salbutamol sulphate conjugate was not available, but extraction into chloroform was assumed to be 100% because Wingstrand & Walle (1984) showed that under the same conditions, the extraction of the closely related compound 4^1-hydroxypropranolol sulphate gave 99% extraction. The identity of the sulphate conjugate was confirmed by the similarity of recovery of salbutamol when the HCl extract was adjusted to pH 5.0 (sodium acetate 1 M) and hydrolysed with arylsulphatase enzyme (600 units, *Helix pomatia*, Sigma) by incubating at

37° C for 120 h. Unchanged salbutamol and salbutamol glucuronide conjugate were not extracted by the tetrabutylammonium sulphate method. Salbutamol glucuronide conjugate in plasma and urine was assayed by first hydrolysing plasma or urine samples with β-glucuronidase enzyme (13,000 units *Helix pomatia*, Sigma) at pH 5.0 (Sorensen's phosphate buffer 0.4 M) by incubating at 37° C for 120 h, and then assaying for unchanged salbutamol as described by Hutchings *et al.* (1983). As no salbutamol glucuronide conjugate was detected in any human plasma or urine samples, the method was developed using glucuronide conjugate excreted in bile of the isolated perfused rat liver preparation, as relatively large quantities of the glucuronide are excreted in rat bile (unpublished observations).

For the intravenous phase, area under the plasma concentration-time curve (AUC) was calculated by the trapezoidal rule with correction for the area beyond the last data point (Gibaldi & Perrier, 1982). The total plasma salbutamol clearance was calculated as the total intravenous dose/AUC(0–∞) and the renal clearance of salbutamol as the cumulative amount of salbutamol excreted unchanged in the urine over 48 h/AUC(0–∞). Elimination half-life was calculated from the slope of the terminal linear portion of the semilogarithmic plot of plasma concentration *vs* time. Apparent volume of distribution was calculated as (total clearance × elimination half-life)/0.693. For the oral phase, AUC during the 8 h dosage interval for unchanged salbutamol and for the sulphate conjugate was calculated by the trapezoidal rule. The systemic availability of salbutamol (F) was calculated from the AUC values for unchanged salbutamol as follows:

$$F = \frac{\text{AUC (0–8h)}_{\text{oral}}}{\text{AUC(0–}\infty\text{)}_{\text{i.v.}}} \times \frac{\text{Total i.v. dose}}{\text{Total oral dose per 8 h}}$$

The renal clearance of salbutamol was calculated as the ratio of the cumulative amount of salbutamol excreted unchanged in the urine during the 8 h dosage interval/AUC(0–8 h) of salbutamol. The renal clearance of the sulphate conjugate was calculated as the ratio of the cumulative amount of sulphate conjugate excreted in urine during the 8 h dosage interval/AUC(0–8 h) of the sulphate conjugate.

Mean results are shown with s.d. Differences between intravenous and oral data were examined by paired Student's t-test. Correlations between variables were examined by Spearman rank correlation, and $P < 0.05$ was considered statistically significant.

Results

Intravenous phase

Mean plasma salbutamol concentration–time curves of the eight subjects who received the 10 μg min^{-1} maintenance infusion are shown in Figure 1a. In spite of the use of a loading dose, steady-state did not appear to have been reached by the end of the 2 h infusion in most subjects. This was supported by the fact that clearance determined as the ratio of maintenance infusion rate/plasma salbutamol concentration at 2 h was significantly greater than that measured as the ratio total intravenous dose/AUC(0–∞). After the end of the infusion, there was an initial distribution phase followed by an elimination phase with a half-life of 3.9 ± 0.8 h (Table 1). Total plasma clearance was 480 ± 123 ml min^{-1} and as the blood/plasma concentration ratio was approximately 1 (0.96 ± 0.13) total blood clearance can be equated with total plasma clearance. The volume of distribution of salbutamol was relatively large (156 ± 38 l), indicating extensive extravascular uptake.

Urinary excretion of both unchanged salbutamol and the sulphate conjugate was complete after approximately 24 h. The majority of the dose was excreted as unchanged salbutamol (64.2 ± 7.1%) and a smaller amount as the sulphate conjugate (12.0 ± 3.1%; Table 1). The renal clearance of salbutamol was 291 ± 70 ml min^{-1}.

There was no significant change in blood pressure, but heart rate did increase with the plasma salbutamol concentration (Figure 1a).

Oral phase

There was no significant difference between the plasma salbutamol concentration at the beginning (6.9 ± 1.5 ng ml^{-1}) and end (6.9 ± 1.1 ng ml^{-1}) of the 8 h dosing interval nor between the plasma concentrations of the sulphate conjugate at the beginning (23.8 ± 8.6 ng ml^{-1}) and end (24.7 ± 10.4 ng ml^{-1}) of the dosing interval. This indicates that plasma concentrations of both salbutamol and sulphate conjugate were at steady-state (Figure 1b). Peak salbutamol concentrations ranged from 10.0–16.9 ng ml^{-1} and occurred from 1.0–4.0 h after the dose. Peak concentrations of the sulphate conjugate ranged from 49.6–120 ng ml^{-1} and occurred at a similar time in each subject (1.00–5.15 h) as the peak salbutamol concentration. Plasma concentrations of the sulphate conjugate greatly exceeded those of the unchanged drug. The mean AUC(0–8 h) of the metabolite was 5.2 times that of salbutamol.

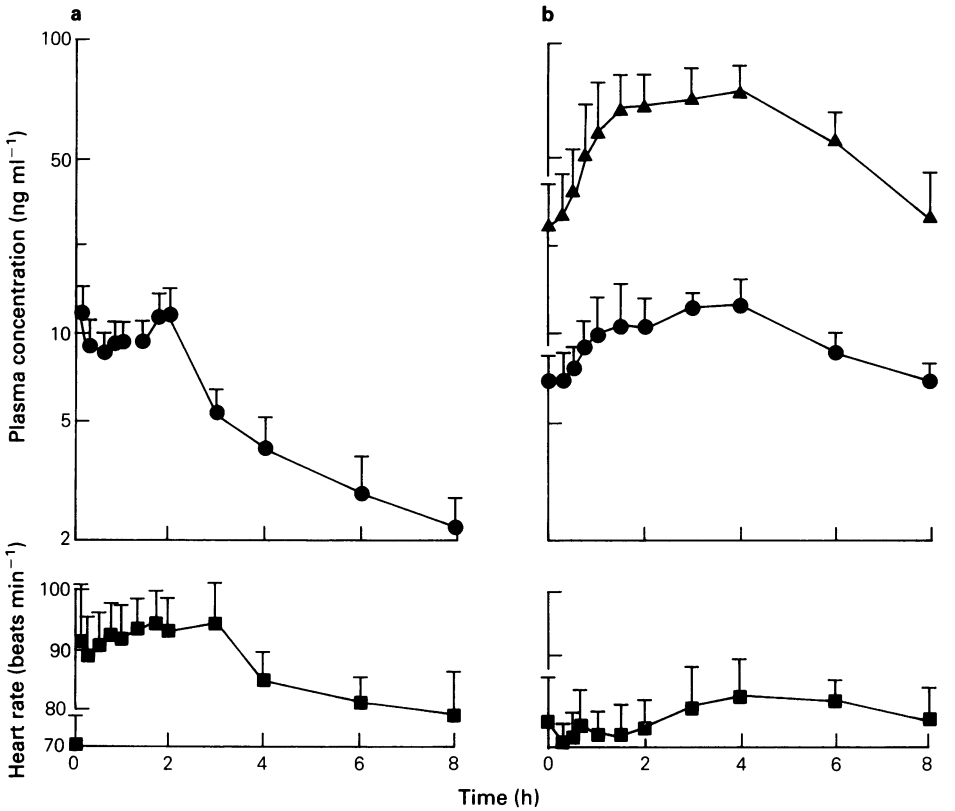

Figure 1 Mean (+ s.d.) plasma concentration of salbutamol (●) and sulphate conjugate (▲) and heart rate (■) (a) in eight subjects who received an intravenous loading dose of 400 μg over 5 min and a maintenance infusion of 10 μg min^{-1} up to 2 h and (b) in 10 subjects during the fourth dosage interval of a 4 mg every 8 h oral regimen.

Table 1 Pharmacokinetics of salbutamol and its sulphate conjugate after i.v. administration. Subjects received a loading dose of 400 μg (200 μg in subjects 1 and 2) over 5 min followed by a constant infusion at 10 μg min^{-1} (5 μg min^{-1} in subjects 1 and 2) for 2 h. Plasma was collected for 8 h and urine for 48 h.

Subject	*Total clearance (ml min^{-1})*	*Elimination half-life (h)*	*Volume of distribution (l)*	*Urinary unchanged salbutamol (% of dose)*	*Urinary sulphate conjugate (% of dose)*	*Salbutamol renal clearance (ml min^{-1})*
1	454	3.0	116	69.9	6.03	317
2	365	4.6	145	69.6	12.5	254
3	504	3.8	164	66.5	11.8	335
4	403	5.4	187	48.1	10.9	194
5	415	4.2	151	64.6	15.2	268
6	649	2.4	135	62.5	15.3	406
7	482	3.7	152	68.8	10.4	332
8	343	4.3	126	63.9	14.1	219
9	734	3.9	248	—	—	—
10	455	3.6	140	—	—	—
Mean	480	3.9	156	64.2	12.0	291
s.d.	123	0.8	38	7.1	3.1	70

The systemic availability of salbutamol was relatively low (0.50 ± 0.04; Table 2).

Significantly less of the salbutamol dose was excreted unchanged in urine (31.8 ± 1.9%; $P < 0.001$) after oral administration and significantly more was excreted as the sulphate conjugate (48.2 ± 7.3%; $P < 0.001$), compared with intravenous administration (Table 2). Renal clearance of salbutamol after oral administration (272 ± 38 ml min^{-1}) was not significantly different from that following intravenous administration, but was significantly greater than creatinine clearance (118 ± 21 ml min^{-1}; $P < 0.01$). Renal clearance of the sulphate conjugate (98.5 ± 23.5 ml min^{-1}) was significantly less than renal clearance of salbutamol and creatinine clearance ($P < 0.05$). There was no correlation between renal clearance of salbutamol and urine flow rate nor between renal clearance of the sulphate conjugate and urine flow rate or creatinine clearance.

There was no significant change in blood pressure, but the heart rate increased with the plasma salbutamol concentration, but to a lesser extent than with intravenous administration (Figure 1).

The plasma protein binding of salbutamol was negligible. At 50 ng ml^{-1}, the binding in pooled blood bank plasma was 8% and at 200 ng ml^{-1} in three healthy volunteers the binding was 7 ± 1%.

Discussion

The mean total plasma clearance of salbutamol was 480 ml min^{-1}. Although not previously reported in the literature it is possible to calculate a mean total clearance from the study of Fairfax *et al.* (1980) in which the mean steady-state plasma salbutamol concentration was reported for seven patients who received a constant rate infusion over 15 h. The calculated clearance from that study is 6.57 ml min^{-1} kg^{-1}, which is comparable to the mean weight adjusted value from the present study (7.72 ml min^{-1} kg^{-1}). The major route of elimination of salbutamol following intravenous administration in the present study was via the kidneys as a mean 64.2% of the dose was excreted unchanged in the urine. Renal clearance of salbutamol (mean 272 ml min^{-1}) was significantly greater than creatinine clearance (mean 118 ml min^{-1}) suggesting that active tubular secretion plays a major role in the renal excretion of salbutamol. The elimination half-life of salbutamol (mean 3.86 h) was within the 2–6 h range reported in previous studies (Fairfax *et al.*, 1980; Lin *et al.*, 1972; Martin *et al.*, 1971; Powell *et al.*, 1985; Walker *et al.*, 1972). Apparent volume of distribution was relatively high (mean 156 l) indicating extensive extravascular distribution.

The pharmacokinetics of orally administered salbutamol were investigated during a dosage interval at steady-state so as to enhance the accurate measurement of plasma salbutamol concentrations. Steady-state was confirmed by the similarity of the pre-dose and 8 h plasma salbutamol concentrations. Plasma concentrations of the sulphate conjugate, which were not detectable after intravenous salbutamol, were also found to be at steady-state during the oral

Table 2 Pharmacokinetics of salbutamol and its sulphate conjugate during the fourth dosage interval of a 4 mg every 8 h oral regimen

Subject	*Urinary unchanged salbutamol (% of dose)*	*Urinary sulphate conjugate (% of dose)*	*Salbutamol renal clearance (ml min^{-1})*	*Sulphate conjugate renal clearance (ml min^{-1})*	*Creatinine clearance (ml min^{-1})*	*Systemic availability*
1	33.0	45.3	280	116	125	0.54
2	32.0	45.0	241	95.1	110	0.49
3	31.0	34.8	285	85.7	99	0.52
4	30.0	46.5	227	64.6	87	0.55
5	35.6	61.8	264	98.4	161	0.44
6	31.8	52.0	318	91.2	123	0.50
7	32.8	47.5	285	148	131	0.45
8	30.8	53.0	221	82.7	105	0.45
9	29.0	47.8	329	105	120	0.49
10	—	—	—	—	—	0.57
Mean	31.8	48.2	272	98.5	118	0.50
s.d.	1.9	7.3	38	23.5	21	0.04

phase of the study. Plasma concentrations of the sulphate conjugate were approximately five times those of salbutamol, which is consistent with previous reports (Evans *et al.*, 1973; Walker *et al.*, 1972). The fact that the elimination rate of the conjugate was similar to that of salbutamol (Figure 1) indicates that the kinetics of elimination of the sulphate conjugate are formation rate-limited.

Following intravenous administration of salbutamol, a mean 64.2% of the dose was excreted unchanged in urine and 12.0% was excreted as the sulphate conjugate. After oral administration only 31.8% of the dose was excreted unchanged while 48.2% was excreted as the sulphate conjugate. These values are similar to those quoted in earlier studies (Evans *et al.*, 1973; Walker *et al.*, 1972). The renal clearance of salbutamol was similar for both routes of administration (Tables 1 and 2) showing that the difference in urinary recovery of unchanged drug was not due to a difference in renal excretion. It has been suggested that the greater formation of sulphate conjugate after oral administration may be due to biotransformation at the first-pass across the gastrointestinal mucosa (Evans *et al.*, 1973; George, 1981). This may be analogous to isoprenaline which has been shown to undergo extensive sulphation in the intestinal wall (George *et al.*, 1974). In the present study, the mean fraction of an oral dose that reaches the systemic circulation was 50%. Studies with tritiated drug have shown that salbutamol is well absorbed from the intestine with 1.2 to 7.0% of the dose recovered in the faeces. (Evans *et al.*, 1973; Martin *et al.*, 1971; Walker *et al.*, 1972). Assuming that the 50% of the 4 mg oral dose reaching the general circulation is handled in the same way as intravenously administered salbutamol, 64.2% of this amount would be expected to be excreted unchanged in the urine (1.28 mg) and 12.0% as the sulphate conjugate (0.48 mg). Assuming 5% of the dose is not absorbed, if the remaining 45% of the oral dose is sulphated entirely in the intestinal wall, this would result in a further 1.8 mg excreted in urine as the sulphate conjugate. Under these circumstances 1.28 mg or 32% of the dose would be excreted unchanged and $0.48 + 1.8 = 2.28$ mg, or 57% of the dose would be excreted as the sulphate conjugate. That these values are similar to those actually observed with oral administration (31.8% unchanged, 48.2% sulphate conjugate, Table 2) strongly suggests that the first-pass elimination of salbutamol is due entirely to sulphate conjugation.

The renal clearance of the sulphate conjugate (98.5 ml min^{-1}) was much less than that of salbutamol (272 ml min^{-1}) and slightly less than that of creatinine (118 ml min^{-1}, $P < 0.05$). This could be taken to indicate that the sulphate conjugate is freely filtered at the glomerulus and that no active secretion occurs. However, as paracetamol sulphate undergoes active tubular secretion (Clements *et al.*, 1984; Morris & Levy, 1983) the relatively low renal clearance of salbutamol sulphate could be due to higher plasma protein binding than the parent drug, as has been suggested for triamterene (Hasegawa *et al.*, 1982).

Salbutamol caused an increase in heart rate with both routes of administration, however the effect was less with oral administration despite similar plasma concentrations. This is presumably due to the development of tolerance during the previous 24 h of salbutamol administration as studies with other β-adrenoceptor agonists have also shown a reduction in the magnitude of chronotropic effect after 24 h continuous intravenous administration (Finley *et al.*, 1984). With both routes of administration the effect on heart rate seemed to lag somewhat behind the change in plasma concentration, suggesting that the chronotropic effect of salbutamol may be associated with a kinetically 'deep' compartment. However, the subjects were supine during the intravenous infusion and assumed the erect posture at the end of the infusion. Therefore, the tachycardia seen at 3 h could have been induced by the change in posture. The study design was not suitable, however, for investigating these possibilities in any detail.

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