Transplacental distribution of salbutamol enantiomers at Caesarian section

David W. Boulton,^{1*} J. Paul Fawcett¹ & Thomas M. Fiddes²

¹School of Pharmacy and ²Department of Obstetrics and Gynaecology, School of Medicine, University of Otago, Dunedin, New Zealand

Aims To investigate the transplacental distribution of salbutamol enantiomers after administration of racemate to women prior to Caesarian section.

Methods Five women about to undergo elective Caesarian section were administered a single 0.25 mg bolus intravenous dose of (R,S)-salbutamol. The time from drug administration to delivery was different for each woman (27–105 min). Maternal and foetal umbilical cord venous blood samples were collected immediately after delivery and the plasma fraction analysed for salbutamol enantiomer concentrations by enantioselective high pressure liquid chromatography.

Results The concentrations (mean $\pm$ s.d.) of the active (R) enantiomer of salbutamol in cord and maternal plasma were 0.46 ± 0.35 and 0.89 ± 0.50 ng ml⁻¹, respectively, and the difference was statistically significant (95% confidence interval (CI) of the difference: 0.12 – 0.74 ng ml⁻¹). The corresponding concentrations of the (S) enantiomer of 0.92 ± 0.45 and 1.11 ± 0.67 ng ml⁻¹, respectively, were not significantly different (95% CI of the difference -0.08 – 0.48 ng ml⁻¹). The ratio of (R):(S) in cord plasma was significantly less than that in maternal plasma ($P=0.016$).

Conclusions Transplacental distribution of salbutamol enantiomers at Caesarian section after prior administration of racemate to mothers leads to concentrations in cord plasma that are significantly less for the active (R) enantiomer and not significantly different for the (S) enantiomer than in maternal plasma presumably due to enantioselective placental-foetal metabolism.

Keywords: Caesarian section, enantiomers, salbutamol, tocolysis, transplacental distribution

Introduction

The treatment of premature labour (tocolysis) to improve foetal outcome remains a therapeutic challenge. Although it has not been possible to date to reverse established labour, the need to mature the foetal lung through the administration of steroids to the mother requires tocolysis for ideally up to 48 h. Current tocolytic therapy in many countries is based on the use of the β_2 -adrenoceptor agonists [1]. The dose of these agents needed to temporarily inhibit labour is relatively high compared with those used in the management of asthma. The high dose tends to produce considerable side-effects in both the mother and the foetus due to β -adrenoceptor stimulation.

Salbutamol (also known as albuterol) is a β_2 -adrenoceptor agonist widely used in tocolysis and occasionally to treat foetal distress resulting from uterine hyperactivity during labour [1]. As with other β_2 -adrenoceptor agonists, salbutamol has an asymmetric carbon atom and therefore can exist as a pair of enantiomers. In clinical practice, it is administered as the racemate (50:50 mixture of enantiomers) despite the fact that only the (R) enantiomer is considered therapeutically active (eutomer) while the (S) enantiomer is considered relatively inactive (distomer) [2]. The disposition of

salbutamol in humans following administration of racemate has been shown to be enantioselective with the eutomer being preferentially metabolized [3–5]. This enantioselectivity has been attributed to a difference in the sulphation of the enantiomers by the 'M' form of phenolsulphotransferase (M-PST) [6]. Little is known about the consequences of this enantioselective disposition in tocolytic therapy.

Salbutamol and other β_2 -adrenoceptor agonists used in tocolysis, such as terbutaline and ritodrine, cross the placenta rapidly following administration to the mother [7–9]. As a result, effects associated with β -adrenoceptor stimulation such as tachycardia, hypotension and hyperglycaemia are observed in the foetus and newborn [1, 10]. The possibility that enantioselective pharmacokinetics of β_2 -adrenoceptor agonists could lead to different relative concentrations of the eutomer in foetal blood implies these drugs could have different side-effect profiles. The aim of this study was to examine the enantioselectivity of the transplacental distribution of salbutamol *in vivo*.

Methods

Patients

Five patients scheduled for elective Caesarian section at the Queen Mary Maternity Unit, Dunedin Hospital, were recruited into the study. Inclusion criteria were: a foetal gestational age of between 37 and 40 weeks; a foetus free of major life-threatening abnormalities; a mother free of major

Correspondence: Dr J. P. Fawcett, School of Pharmacy, University of Otago, P.O. Box 913, Dunedin, New Zealand.

*Present address: Department of Cell and Molecular Pharmacology and Experimental Therapeutics, Medical University of South Carolina, 171 Ashley Avenue, Charleston, South Carolina 29425, United States of America.

Patient number	Age (years)	Mother		Newborn	
		Weight (kg)*	Anaesthesia	Gestational age (weeks)	Weight (kg)
1	43	93	Epidural	38	3.37
2	20	98	Spinal	39	3.71
3	37	76	Epidural	37	3.12
4	35	70	Spinal	38	4.32
5	34	68	General	39	2.62
Mean $\pm$ s.d.	33 $\pm$ 8	81 $\pm$ 14		38 $\pm$ 1	3.43 $\pm$ 0.64

*Weight within 1 week prior to delivery.

Patient	Time interval (min)*	(R)-salbutamol (ng ml ⁻¹)		(S)-salbutamol (ng ml ⁻¹)	
		Maternal	Cord	Maternal	Cord
1	27	1.56	1.06	2.14	1.56
2	60	0.28	0.13	0.44	0.42
3	89	1.18	0.44	1.23	1.03
4	89	0.56	0.35	0.60	0.55
5	105	0.88	0.32	1.16	1.03
Mean $\pm$ s.d.	74 $\pm$ 31	0.89 $\pm$ 0.50	0.46 $\pm$ 0.35	1.11 $\pm$ 0.67	0.92 $\pm$ 0.45
95% CI of difference		0.12–0.74		–0.08–0.48	
P value		0.018		0.124	

*Time between drug administration and delivery.

Table 1 Patient details for mothers and newborns and anaesthesia involved in Caesarian section.

Table 2 Maternal and cord plasma concentrations of salbutamol enantiomers at delivery following intravenous administration of (R,S)-salbutamol (0.25 mg) to the mother.

chronic disease during pregnancy; a mother who had not been treated with antihypertensive agents, insulin, hypoglycaemic agents, chronic steroid therapy or any other tocolytic agent during pregnancy. Recent or current treatment with antibiotics did not preclude entry into the study. The study protocol was approved by the Southern Regional Health Authority Ethics Committee (Otago) and written informed consent was obtained from the mothers prior to entry into the study.

Drug administration

An intravenous bolus of 0.25 mg racemic salbutamol as the sulphate salt in normal saline (Ventolin®, Allen and Hanburys Ltd, Greenford, UK) was administered *via* an indwelling catheter in an antecubital vein. Patients received the drug at various times up to 2 h prior to anticipated delivery. Within 10 min of delivery, blood samples (up to 7 ml) were collected into heparinized glass tubes (Vacutainer®, Becton Dickinson, Rutherford, NJ, USA), one from the umbilical cord vein and one from the mother using the opposite arm to that used for drug administration.

Enantioselective assay

Blood samples were centrifuged and the plasma aspirated into plastic sample tubes and stored at -80°C until analysis. Plasma samples (up to 4 ml) were analysed for salbutamol enantiomers by enantioselective normal phase high performance liquid chromatography as previously described [3]. The limit of detection of the assay was 620 pg ml⁻¹ from a 1 ml

plasma sample. Intraday and interday variation of the assay was 3.0 and 7.4%, respectively.

Data analysis

Data are reported as mean $\pm$ standard deviation (s.d.). Differences in enantiomer concentrations within and between maternal and cord plasma were examined by paired two-tailed Student's *t*-tests (SigmaStat—version 1.0, Jandel Corp., San Rafael, CA, USA). The level of significance was set at $P=0.05$ and 95% confidence intervals (CI) of the differences are given.

Results

Patient details for mothers and newborns and anaesthesia involved in Caesarian section are shown in Table 1. Maternal and cord plasma concentrations of the two enantiomers are shown in Table 2. The concentration of (R)-salbutamol was significantly higher in maternal plasma than in cord plasma ($P=0.018$) but the concentration of (S)-salbutamol was not significantly different. The concentration of (R)-salbutamol in cord and maternal plasma was less than the corresponding concentration of (S)-salbutamol, consistent with earlier studies in normal volunteers [3–5]. However, the difference between enantiomer concentrations was only significant for cord plasma ($P=0.008$). There was no apparent correlation between cord or maternal plasma concentration and time from drug administration for either enantiomer but concentrations were generally less the longer the time between drug administration and delivery.

The maternal (R):(S) ratio (0.85 ± 0.14) was significantly higher than the cord ratio (0.47 ± 0.17) [$P=0.016$]. The cord to maternal ratio for (R)-salbutamol (0.50 ± 0.14) was significantly less than that of (S)-salbutamol (0.87 ± 0.09) [$P=0.015$]. The cord: maternal ratio based upon the sum of enantiomers (total salbutamol concentration) was 0.68 ± 0.08 .

Discussion

Placental transfer of drugs is a complex process dependent on the physicochemical properties of the drug and on its metabolism. The lower concentration of salbutamol in cord compared with maternal plasma found in this study ($68 \pm 8\%$) and in a previous nonchiral study (up to 50%) [8] is consistent with the ionized state of salbutamol at physiological pH and its intermediate molecular weight. The relative concentration of enantiomers in foetal blood is also affected by maternal and foetal enantioselective metabolism and by the time elapsed between administration of racemate and sample collection.

Although the human foetus has limited oxidative and glucuronidative capacity, the deficit is counterbalanced by a larger capacity for sulphate conjugation [11]. In humans, metabolism of salbutamol appears to be exclusively *via* sulphation to an inactive conjugate [6, 12]. Early development of substantial sulphation capacity is consistent with the results of a nonchiral study of salbutamol disposition in infants with bronchopulmonary dysplasia, where the drug had a shorter half-life in the study group [13] than in healthy adult volunteers [12, 14]. In addition to enantioselective metabolism by the foetus, there may also be a contribution from the placenta since β_2 -adrenoceptor agonist metabolizing PST enzymes have been demonstrated in nonchiral studies of placental tissue homogenate metabolism [15, 16].

The (R):(S) salbutamol ratio within an individual mother or foetus is indicative of the extent of their enantioselective metabolism. The cord ratio was found to be smaller than the maternal ratio suggesting the placental-foetal unit has a good capacity for salbutamol sulphation. The concentration of (S)-salbutamol appears to reach an 'equilibrium' between maternal and cord blood within an hour after administration since patients 2–5 show approximately equal concentrations in the maternal and cord blood (see Table 2). Preliminary data suggest the enantioselective transplacental distribution observed in this study is not due to enantioselective plasma protein binding [17].

Another β_2 -adrenoceptor agonist commonly employed as a tocolytic agent, terbutaline, has also been shown to undergo enantioselective metabolism in humans almost exclusively by M-PST [18, 19]. In contrast to salbutamol, the metabolism of terbutaline by M-PST leads to a predominance of the eutomer in the systemic circulation [20, 21]. On this basis, the (R):(S) ratio in cord blood would be expected to be larger for terbutaline than for salbutamol. This possibility, coupled with evidence that the total concentration of terbutaline is higher in cord plasma than in maternal plasma [10], suggests an equivalent dose of terbutaline would produce more severe β -mediated side-effects in the foetus than seen with salbutamol. Clinical evidence to support this hypothesis is difficult to obtain as

crossover studies examining relative side-effects in the foetus cannot be carried out.

This study has shown that cord blood concentrations of the eutomer of salbutamol are significantly lower than maternal blood concentrations both in absolute terms and relative to the distomer. This is probably due to enantioselective metabolism by the placenta, foetus or both resulting in a certain 'protection' of the foetus from β -mediated side-effects of the eutomer. The implication of the relatively higher concentration of the distomer of salbutamol in foetal blood and the potential benefits of a pure eutomer formulation await further clarification.

The authors would like to thank Dr Sarah Tout for clinical assistance and the New Zealand Pharmacy Education and Research Foundation and the University of Otago Research Committee for their financial support.

References

- Caritis SN. Treatment of preterm labour: a review of the therapeutic options. *Drugs* 1983; **26**: 243–261.
- Brittain RT, Farmer JB, Marshall RJ. Some observations on the β -adrenoceptor agonist properties of the isomers of salbutamol. *Br J Pharmacol* 1973; **48**: 144–147.
- Boulton DW, Fawcett JP. Determination of salbutamol enantiomers in human plasma and urine by chiral high-performance liquid chromatography. *J Chromatogr B* 1995; **672**: 103–107.
- Boulton DW, Fawcett JP. Enantioselective disposition of salbutamol in man following oral and intravenous administration. *Br J Clin Pharmacol* 1996; **41**: 35–40.
- Boulton DW, Fawcett JP. Pharmacokinetics and pharmacodynamics of single oral doses of albuterol and its enantiomers in humans. *Clin Pharmacol Ther* 1997; **62**: 138–144.
- Walle UK, Persola GR, Walle T. Stereoselective sulphate conjugation of salbutamol in humans: comparison of hepatic, intestinal and platelet activity. *Br J Clin Pharmacol* 1993; **35**: 413–418.
- Bergman B, Bokström H, Borga O, Enk L, Hedner T, Wängberg B. Transfer of terbutaline across the human placenta in late pregnancy. *Eur J Resp Dis* 1984; **65** (Suppl 134): 81–86.
- Dellenbach P, Guikovsky JP, Munch F, Ragon A, Schlewer G, Wolff. Passage transplacentaire d'un anesthésique et d'un β -mimétique: intérêt des isotopes stables et de la spectrométrie. *Pharmacologie Périnatale* 1977; **10**: 55–77.
- Gross TL, Kuhnert BR, Kuhnert PM, Rosen MG, Kazzi NJ. Maternal and fetal plasma concentrations of ritodrine. *Obstet Gynecol* 1985; **65**: 779–793.
- Ingemarsson I, Westgren M, Lindberg C, Åhrén B, Lundquist I, Carlsson C. Single injection of terbutaline in preterm labor: Placental transfer and effects on maternal and fetal carbohydrate metabolism. *Am J Obstet Gynecol* 1981; **139**: 697–700.
- Rane A, Tomson G. Prenatal and neonatal drug metabolism in man. *Eur J Clin Pharmacol* 1980; **18**: 9–15.
- Morgan DJ, Paull JD, Richmond BH, Wilson-Evered E, Ziccone SP. Pharmacokinetics of intravenous and oral salbutamol and its sulphate conjugate. *Br J Clin Pharmacol* 1986; **22**: 587–593.
- Kirpalani H, Koren G, Schmidt B, Tan Y, Santos R, Soldin S. Respiratory response and pharmacokinetics of intravenous

- salbutamol in infants with bronchopulmonary dysplasia. *Crit Care Med* 1990; **18**: 1374–1377.
- 14 Goldstein DA, Tan YK, Soldin SJ. Pharmacokinetics and absolute bioavailability of salbutamol in healthy adult volunteers. *Eur J Clin Pharmacol* 1987; **32**: 631–634.
 - 15 Sodha RJ, Glover V, Sandler M. Phenolsulphotransferases in human placenta. *Biochem Pharmacol* 1983; **32**: 1655–1657.
 - 16 Sodha RJ, Schneider H. Sulphate conjugation of β_2 -adrenoceptor stimulating drugs by platelet and placental phenol sulphotransferase. *Br J Clin Pharmacol* 1984; **17**: 106–108.
 - 17 Boulton DW, Fawcett JP. Enantioselective disposition of albuterol in humans. *Clin Rev Allergy Immunol* 1996; **14**: 115–138.
 - 18 Walle T, Walle UK. Stereoselective sulphate conjugation of racemic terbutaline by human liver cytosol. *Br J Clin Pharmacol* 1990; **30**: 127–133.
 - 19 Walle T, Walle UK. Stereoselective sulphate conjugation of 4-hydroxypropranolol and terbutaline by the human liver phenolsulfotransferases. *Drug Metab Dispos* 1992; **20**: 333–336.
 - 20 Borgström L, Nyberg L, Jonsson S, Lindberg C, Paulson J. Pharmacokinetic evaluation in man of terbutaline given as separate enantiomers and as the racemate. *Br J Clin Pharmacol* 1989; **27**: 49–56.
 - 21 Borgström L, Kennedy BM, Nilsson B, Angelin B. Relative duodenal absorption of the two enantiomers of terbutaline after duodenal administration. *Eur J Clin Pharmacol* 1990; **38**: 621–623.

(Received 4 April 1997,
accepted 16 July 1997)