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Distribution and excretion of sumatriptan in human milk

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1 The excretion of a 6 mg subcutaneous dose of sumatriptan in breast milk was studied in five lactating volunteer subjects with a mean age of 27.6 years and a mean body weight of 75 kg. Drug concentrations in milk and plasma over the ensuing 8 h were measured by high-performance liquid chromatography.

2 The mean milk:plasma ratio estimated from the areas under the milk and plasma concentration-time curves (AUC) was 4.9 (95% CI 4.1–5.7), indicating a significant transfer of sumatriptan into the milk compartment.

3 The mean total recovery of drug in milk was estimated to be only 14.4 μg (95% CI 6.1–22.7 μg), or 0.24% of the 6 mg administered dose. On a weight-adjusted basis this corresponded to a mean infant exposure of 3.5% of the maternal dose (95%CI 0.3–6.7%).

4 If oral bioavailability in the infant is similar to that in adults (14%), the weight-adjusted infant dose is reduced to 0.49%. Furthermore, allowance for reduced clearance in the infant predicts an infant exposure varying from 4.9% in a very premature neonate to 0.7% in a 30 week old infant.

5 Since sumatriptan is usually administered as a single dose at infrequent intervals, the low level of excretion in breast milk suggests that continued breast feeding following its use will not pose a significant risk to the suckling infant. Even this minor exposure could be largely avoided by expressing and discarding all milk for 8 h after the dose.

Keywords sumatriptan breast milk pharmacokinetics milk:plasma ratio lactation

Introduction

Sumatriptan is a selective agonist at 5-HT_1 vascular receptors [1,2] and a highly effective new drug for the treatment of migraine [1,3,4]. It can be administered either orally or by subcutaneous (s.c.) injection and relieves the acute symptoms of migraine in 50–86% of patients[1]. The drug has a short half-life ($t_{1/2}$) of around 2 h in humans [1,5], and is mainly excreted in the urine as the indole acetic acid metabolite, which has no significant 5-HT_1 agonist activity [5]. Sumatriptan is a weak base with a pKa of 9.63 at the tertiary nitrogen and another of >12 at the sulphonamido nitrogen [6]. Oral bioavailability is around 14% [1,5] while s.c. bioavailability is essentially complete [7]. It has a volume of distribution (V_z) of around 170 l in adult humans [1,5]. Studies in rodents indicate that there is significant transfer into milk [6]. In the present study we have quantified the extent of the distribution of sumatriptan in human milk, in order to evaluate the exposure risk for the suckling infant of a migraineur treated with the drug.

Methods

Materials

Sumatriptan and *N*-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulphonamide hydrochloride (GR855-48) reference materials were obtained from Glaxo Australia Pty Ltd, Boronia, Australia.

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Subjects

Five lactating women with a mean age of 27.6 years (range 24–34 years) and a mean body weight of 75 kg (range 69–86 kg) participated in the study. The mean duration of lactation was 22.2 weeks (range 10.8–28.4). At the time of study, their nursing infants had a mean body weight of 6.1 kg (range 3.6–8.0 kg).

Study protocol

Subjects had a medical examination and an electrocardiograph (ECG) prior to inclusion in the study, to exclude the presence of pre-existing cardiovascular disease. They were required to fast for 8 h prior to the commencement of the study. On the study day, an indwelling cannula was inserted into a forearm vein, and the 6 mg dose of sumatriptan was administered s.c. at approximately 08.00 h. Subjects were given a standard light breakfast at 10.00 h and lunch at 12.30 h. Blood samples for sumatriptan analysis were drawn at 0, 5, 10, 15, 20, 30 and 45 min and 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 h after the dose. Milk was obtained by emptying both breasts with a breast pump just prior to the dose and at hourly intervals thereafter for 8 h. Mean milk volumes at each collection were 48.6, 49.6, 21.4, 41.0, and 21.6 ml for subjects 1 through 5 respectively. Heart rate and blood pressure were monitored before dosing and 0.5, 1, 2 and 8 h after the dose. The infants were bottle fed with stored mother's milk during the study. The study design was approved by the Research and Ethics Committees of the King Edward Memorial Hospital for Women and all subjects gave written informed consent to their participation.

Drug analysis

Sumatriptan in plasma was measured by high performance liquid chromatography (h.p.l.c.) with electrochemical detection based on the method of Andrew *et al.* [8], with substantial modifications. Briefly, after addition of GR85548A (100 ng; internal standard) to 1 ml plasma and extraction into 5 ml of 20% v/v dichloromethane in ethyl acetate, analytes were back extracted into 0.2 ml of 0.1 M KH_2PO_4 (pH 5). The aqueous phase was washed with 5 ml hexane and aliquots (50 µl) were injected onto the h.p.l.c. The h.p.l.c. column used was a Merck LiChrospher 60 RP Select B (4.6 mm i.d. × 250 mm) together with a mobile phase of 22% v/v acetonitrile in 0.02 mM phosphate buffer (pH 7), pumped at a flow rate of 1 ml min^{-1}. Under these conditions, the approximate retention times for sumatriptan and GR85548A were 4 and 10.2 min respectively. The intra-day coefficients of variation at 2 and 40 µg l^{-1} were 3.4 and 1.4% respectively ($n=5$), and the standard curve was linear up to 100 µg l^{-1}. Analysis of sumatriptan in milk also was carried out using the method of addition and a four point standard curve as previously described [9], together with the extraction and h.p.l.c. methods described above. The intra-day coefficients of variation at 2 and 40 µg l^{-1} were 5.4 and 3.1% respectively ($n=5$), and the standard curve was linear up to 100 µg l^{-1}. The limit of detection in both matrices was 1 µg l^{-1}.

Measurement of octanol:buffer pH 7.4 partition coefficient

The partition of sumatriptan (0.1 mg l^{-1}) between octanol and 0.02 M Sorensen's phosphate buffer was measured as previously described [9] with quantification in the aqueous phase by h.p.l.c. as above.

Data analysis

Plasma and milk concentration-time curves were analysed by a noncompartmental pharmacokinetic method using the program TOPFIT [10]. Elimination half-life was determined from log-linear regression analysis of the last five data points for plasma and the last four data points for milk. The peak concentration and the time of peak for milk and plasma were determined from the primary data. Plasma clearance (CL = dose/ area under the plasma concentration-time curve (AUC)), volume of distribution ($V_z = CL/\lambda_z$, where λ_z is the terminal elimination rate constant) and mean residence time (MRT = AUMC/AUC) were estimated from the plasma and milk data as appropriate [10]. Areas under the plasma- and milk-concentration time data (AUC) were measured by the linear trapezoidal rule, with extrapolation to infinity estimated as the last plasma or milk concentration divided by the respective elimination rate constant. In the AUC analysis milk concentration data were plotted relative to the mid-point of each collection period. Cumulative excretion in milk (Σ volume at each collection × sumatriptan concentration in sample) was calculated to facilitate estimation of the total infant exposure. Data have been summarised as mean and 95% confidence interval, or mean and range, as appropriate with differences between means evaluated by a *t*-test.

Results

There were no clinically significant changes in either blood pressure or heart rate (data not shown) following the s.c. administration of sumatriptan. All subjects reported some mild adverse effects such as flushing, light-headedness, throat or chest tightness and nausea. However, the effects resolved within 2 h in all cases.

At physiological pH, sumatriptan partitioned poorly into octanol, with a log $P_{\text{octanol:buffer pH 7.4}}$ value of −1.2. The mean volume of milk collected during the 8 h of the study was 269 ml (range 157–430 ml). This corresponds to a mean daily milk production of 807 ml which is similar to that quoted for women in the first year of lactation [11], or to a mean of 155 ml kg^{-1} infant body weight per day. Typical plasma and milk concentration-time data, and cumulative milk excretion

data for subject 2 are shown in Figure 1, and mean pharmacokinetic descriptors for all subjects are summarised in Table 1. In the plasma, the mean maximum concentration (C_{max}) of 80.2 μg l^{-1} occurred some 16 min (t_{max}) after dose, while for the milk, the mean peak concentration 87.2 μg l^{-1} was delayed until approximately 2.6 h after dose. Sumatriptan was below the 1 μg l^{-1} detection limit in all plasma samples taken after 6 h. The mean plasma $t_{1/2}$ of 1.3 h was significantly lower ($t=2.33$, $P=0.048$) than that of 2.2 h calculated from the milk data. Thus, the slightly longer $t_{1/2}$ for milk most likely reflects the late time of peak and a lack of data at time points later than 8 h. Clearance (0.91 l h^{-1} kg^{-1}) and V_2 (1.69 l kg^{-1}) for the plasma data following s.c. administration were similar to previously reported values [3,7]. The mean milk:plasma ratio calculated from AUC data was 4.9 (95% CI 4.1–5.7) indicating a significant transfer of sumatriptan into the milk compartment. However, the mean cumulative excretion of sumatriptan in milk over the 8 h of the study was only 12.6 μg (95% CI 4.6–20.5 μg) showing that only 0.21% of the administered dose is excreted in the milk. Extrapolation of the AUC for the milk concentration-time curve, from the last collection at 8 h to infinity, increased the AUC by a mean of only 13.6% (range 3.8–19.6%). If an individual AUC correction factor is applied to the cumulative excretion data to 8 h for each subject, then mean total recovery of drug to infinity would be predicted to increase to 14.4 μg (95% CI 6.1–22.7 μg), or 0.24% of the total 6 mg dose which was administered to the subjects. Alternatively, if one calculates individual infant dose as cumulative excretion in milk to infinity divided by the infant's body weight (μg sumatriptan kg^{-1}) and expresses this figure as a percent of the individual maternal dose in μg kg^{-1}, the mean weight-adjusted dose for the infants would have been 3.5% (95% CI 0.3–6.7%).

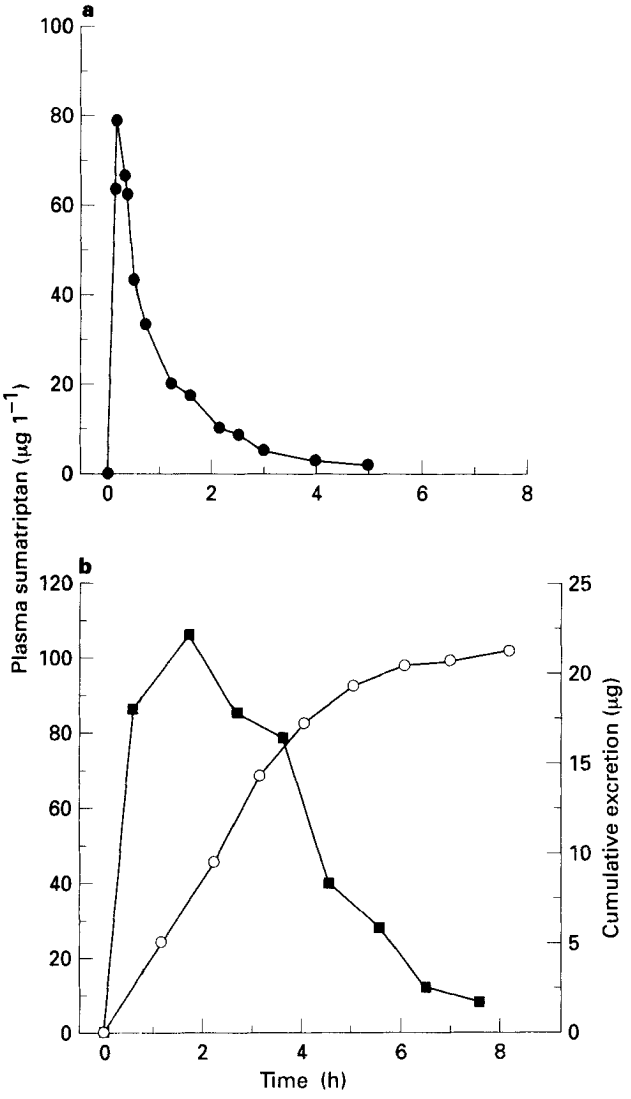

Figure 1 Plasma concentration-time data (panel a; ●) and milk concentration-time data (panel b; ■) for subject 2 following a single 6 mg s.c. dose of sumatriptan. Panel b (right ordinate axis; ○) also shows the cumulative excretion of sumatriptan in the milk over the 8 h collection period.

Table 1 Pharmacokinetic parameters (mean; 95% CI) estimated from plasma and milk concentration-time data following 6 mg sumatriptan s.c. to five subjects.

Parameter	*Plasma*	*Milk*
C_{max} (μg l^{-1})	80.2 (62.4–98.1)	87.2 (61.9–112.5)
t_{max} (h) *	0.25 (0.15–0.33)	2.5 (1.69–3.53)
$t_{1/2}$(h)	1.3 (0.75–1.85)	2.22 (1.16–3.1)
MRT (h)	1.47 (1.12–1.82)	4.33 (3.25–5.41)
CL (l h^{-1} kg^{-1}) **	0.91 (0.84–1.01)	—
V_z (l kg^{-1})	1.69 (1.34–2.34)	—
AUC (μg l^{-1} h)	89.1 (79.3–98.8)	432 (372–493)

* median (range)

** assuming bioavailability is essentially complete [7]

Discussion

Plasma pharmacokinetic descriptors for the s.c. administration of 6 mg sumatriptan were in agreement with previous literature values [5]. Our study is the first to report the pharmacokinetics of sumatriptan in human milk. The broad elevated concentration-time profile between 1–5 h (generally > 50 μg l^{-1}), with a mean time of peak concentration in the milk of 2.6 h, was unexpected. However, others have shown that following oral administration, peak plasma concentrations do not occur until 1–4 h after dose [5,7,12]. They suggested that the late peak was in part due to extensive first-pass metabolism and in part due to incomplete absorption. Difficulty in crossing lipoprotein membranes also is suggested by the finding that the drug does not cross the blood brain barrier in rodents [13]. At physiological pH, sumatriptan is some two pH units below its major pK_a, and will be highly ionised. It will therefore partition poorly into lipoprotein membranes as is reflected by its low log P value (−1.243). Thus, while difficulty in traversing lipoprotein membranes may contribute to the broad peaks which we observed in the milk concentration-time profiles, it seems unlikely to offer a complete explanation.

M:P concentration ratios determined from single observations in one or more patients frequently have been used to estimate transfer of a range of drugs and hence estimate infant exposure [14]. However, for a drug such as sumatriptan which has a short $t_{1/2}$ and delayed time of peak, such calculations will yield highly variable time-dependent values. In such cases, calculation of the M:P ratio based on AUC data has been recommended to achieve reliable data [15–17]. In our study, M:P ratios calculated using AUC data for sumatriptan give a mean value of 4.9 which is high by comparison with values for most other basic drugs [14,18]. This value also is approximately three times greater than the theoretical M:P ratio of 1.6, which can be calculated using the pH-partition hypothesis [19], with a pK_a of 9.63 (tertiary N) and plasma and milk pH values of 7.4 and 7.2 respectively. If one modifies this calculation as suggested by Begg *et al.* [16], a theoretical M:P ratio of 2.6 or approximately 50% of the observed value is obtained. The latter calculation is most affected by milk pH and predicts ratios varying from 4.7 to 25.4 for a pH range of 7 to 6.8 respectively. Although a milk pH of 7.2 has been widely accepted in the literature[18], recent studies show that mean milk pH ranges from 6.7–6.9 during the first year of lactation [11]. Therefore, it seems likely that the high M:P ratio observed for sumatriptan is largely due to the lower than expected milk pH. Unfortunately, we did not measure pH in the present study. Log P for sumatriptan is low and makes little contribution to the calculated milk transfer, while protein binding in milk is also unlikely to be a major factor if its value in adult plasma (14–21%; [3]) is a reliable guide.

It should be noted that our mean estimate of $t_{1/2}$ for sumatriptan in milk was slightly but significantly greater than that for the drug in plasma. Since the $t_{1/2}$ is used in calculating the extrapolated portion of the AUC values, it could be argued that we may have overestimated milk AUC and hence the M:P ratio. However, on average the extrapolated portion of the AUC was only 13.7% of the total AUC and use of the shorter plasma $t_{1/2}$ value in the calculation only reduces the M:P ratio to 4.6.

Considering that the usual mode of administration of sumatriptan is as a single dose given at infrequent intervals, we suggest that the cumulative excretion of a single dose of the drug in milk provides a robust way of assessing infant exposure. On this basis, our data show that a nursing infant who continued to breast feed following a 6 mg s.c. maternal dose, would receive a maximum of 3.5% of the maternal dose on a weight adjusted basis. If the low oral bioavailability of sumatriptan (14%) in adults [3,5] can be applied in the infant, the level of exposure following a single maternal dose will be further reduced to 0.03% of the absolute maternal dose or 0.49% on a weight adjusted basis. The impact of this oral dose in an infant must be considered according to the likely clearance values at various post-conceptual ages [16]. In a very premature infant (post conceptual age 28–34 weeks) where clearance is likely to be only one tenth of the adult value, infant exposure could be as high as 4.9% on a weight adjusted basis. At birth, 6 and 30 weeks of age, weight adjusted exposure would be reduced to 1.5%, 1% and 0.7% respectively. These dose rates are low and in our view are likely to have little of or no pharmacological effect. Nevertheless, after a single s.c. maternal dose of sumatriptan, infant exposure could be avoided almost completely by expressing and discarding all milk for an 8 h period. Longer withholding periods may be appropriate if a second dose was given within 12 h.

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References

1 Plosker GL, McTavish D. Sumatriptan. A reappraisal of its pharmacology and therapeutic efficacy in the acute treatment of migraine and cluster headache. *Drugs* 1994; **47:** 622–651.

2 Humphrey PP, Feniuk W. Mode of action of the anti-migraine drug sumatriptan. *Trends Pharmacol Sci* 1991; **12:** 444–446.

3 Fullerton T, Gengo FM. Sumatriptan: a selective 5-hydroxytryptamine receptor agonist for the acute treatment of migraine. *Annals Pharmacother* 1992; **26:** 800–808.

4 Ferrari MD, Saxena PR. Clinical and experimental effects of sumatriptan in humans. *Trends Pharmacol Sci* 1993; **14:** 129–133.

5 Fowler PA, Lacey LF, Thomas M, Keene ON, Tanner RJ, Baber NS. The clinical pharmacology, pharmacokinetics and metabolism of sumatriptan. *Eur Neurol* 1991; **31:** 291–294.

6 Glaxo Australia Pty Ltd. Data on file for sumatriptan. 1993.

7 Lacey LF, Hussey EK, Fowler PA. Single dose pharmacokinetics if sumatriptan in healthy volunteers. *Eur J Clin Pharmacol* 1995; **47:** 543–548.

8 Andrew PD, Birch HL, Phillpot DA. Determination of sumatriptan succinate in plasma and urine by high-performance liquid chromatography with electrochemical detection. *J Pharm Sci* 1995; **82:** 73–76.

9 Ilett KF, Lebedevs TH, Wojnar-Horton RE, *et al.* The excretion of dothiepin and its primary metabolites in breast milk. *Br J Clin Pharmacol* 1993; **33:** 635–639.

10 Thomann P. *Non-compartmental analysis methods manual. TOPFIT Version 2* Pharmacokinetic and pharmacodynamic data analysis system for the PC. Heinzel G, Woloszczak R, and Thomann P. Gustav Fischer, Stuttgart, 1993; Part 2, pp 5–66.

11 Allen JC, Keller RP, Archer P, Neville MC. Studies in human lactation: milk composition and daily secretion rates of macronutrients in the first year of lactation. *Am J Clin Nutr* 1991; **54:** 69–80.

12 Dixon CM, Saynor DA, Andrew PD, Oxford J, Bradbury A, Tarbit MH. Disposition of sumatriptan in laboratory animals and humans. *Drug Metab Dispos* 1993; **21:** 761–769.

13 Humphrey PPA, Wasyl F, Perren MJ, Skingle M, Beresford IJM, Whalley ET. Serotonin and migraine. *Ann NY Acad Sci* 1990; **600:** 587–600.

14 Bennett PN, and the WHO Working Group. *Drugs and human lactation.* First edn. Elsevier, Amsterdam, 1988.

15 Begg EJ, Atkinson HC. Partitioning of drugs into human milk. *Ann Acad Med Singapore* 1991; **20:** 51–55.

16 Begg EJ, Atkinson HC, Duffull SB. Prospective evaluation of a model for the prediction of milk: plasma drug concentrations from physicochemical characteristics. *Br J Clin Pharmacol* 1992; **33:** 501–505.
17 Begg EJ, Atkinson HC. Modelling of the passage of drugs into milk. *Pharmacol Ther* 1993; **59:** 301–310.
18 Atkinson HC, Begg EJ. Prediction of drug distribution into human milk from physicochemical characteristics. *Clin Pharmacokinet* 1990; **18:** 151–167.
19 Wilson JT. *Drugs in breast milk.* ADIS Press, Sydney,1981.

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