The excretion of zopiclone into breast milk

I. MATHESON¹, H. A. SANDE² & J. GAILLOT³

¹Department of Pharmacotherapeutics, University of Oslo, Oslo, ²Department of Gynecology and Obstetrics, Ullevaal Hospital, Oslo, Norway and ³Institute of Biopharmacy, Antony, France

1 The excretion of zopiclone into breast milk was studied in 12 lactating women in the early postpartum period following the oral administration of a single zopiclone tablet (7.5 mg).

2 The milk/plasma AUC ratio of zopiclone was 0.51 ± 0.09 (mean $\pm$ s.d.). Individual mean milk/plasma concentration ratios of zopiclone showed significant interindividual variation (range 0.41 – 0.70).

3 A comparison of pharmacokinetic parameters in the postpartum women with those reported previously in non-pregnant women, showed significantly higher $C_{\max}$ values in the lactating mothers; $t_{\max}$ occurred later in milk than in maternal plasma.

4 Assuming a daily milk intake of 0.15 l kg^{-1} and 100% absorption the average infant dose of zopiclone in milk would be 1.4% of the weight adjusted dose ingested by the mother.

Keywords zopiclone breast milk breast-feeding pharmacokinetics

Introduction

The extent of the prescribing of hypnotics to lactating women in maternity wards has been questioned because of the possibilities of residual psychomotor effects in the mother and drug excretion into breast milk (Matheson, 1985; Passmore *et al.*, 1984). In 1981 81% of Norwegian maternity wards offered hypnotics routinely and 41–86% of the women took hypnotics postpartum, predominantly nitrazepam (Matheson, 1989).

Zopiclone is a cyclopyrrolone hypnotic which, although structurally unrelated to the benzodiazepines, shares their pharmacological profile (Goa & Heel, 1986; Wickstrøm & Giercksky, 1980). Pharmacokinetic studies (Gaillot *et al.*, 1983) have demonstrated a bioavailability of 75%, a short elimination half life (4–5 h), 45% binding to plasma proteins and a volume of distribution of 1.51 l kg^{-1} . As a result of extensive metabolism only 7–10% of the dose is recovered in urine and faeces as unchanged compound.

The only active metabolite, zopiclone *N*-oxide, is assumed to exert 50% of the activity of the parent drug (Gaillot *et al.*, 1983; Houghton *et al.*, 1985). Since all drugs will appear in breast milk to some extent, care should be taken to assess the transfer of a drug which might be prescribed to nursing women. The aim of this study was to describe the time-course of zopiclone in milk and plasma in the early lactation period, and to calculate the exposure of infants to the drug.

Methods

Subjects

Written informed consent was obtained from 12 healthy, lactating women between 2 and 6 days postpartum. The women were allowed additional analgesic medication as required and nursing

was interrupted until 07.00 h the next morning, as preliminary studies had shown low zopiclone concentrations in human milk (Gaillot *et al.*, 1983). Half of the women delivered by Caesarean section, the other half by the vaginal route. All of them had initiated breast-feeding. The study was approved by the Hospital Drug and Therapeutics Committee, and notified to the Norwegian Medicines Control Authority.

Study design

Each subject took 7.5 mg zopiclone by mouth in the supine position at 21.00–23.00 h. Venous blood (5 ml) and milk samples (5–10 ml) were obtained at 0.25, 0.5, 1, 2, 4, 8, 11 and 22 h after the tablet was swallowed. Additional milk samples were taken after 3, 6 and 15 h. Milk from both breasts was collected with a pump and blood was taken from an indwelling catheter. After immediate centrifugation the samples were frozen at -20°C pending analysis. Routine laboratory tests were carried out before and after the study.

Assay

Zopiclone was assayed by h.p.l.c. as described by Gaillot *et al.* (1983). In brief, zopiclone was extracted from milk into dichloromethane: diethylether (1:2) before separation and fluorimetric detection. The limit of the assay was $2\text{ }\mu\text{g l}^{-1}$ for plasma and milk and the coefficients of variation ranged from 1.6–2.5% (plasma) and 1–10% (milk). Zopiclone was stable in plasma and milk throughout the study period (5 weeks).

Pharmacokinetic analysis

The drug elimination half-life ($t_{1/2}$) was calculated from the slope (k) of the regression line fitted to a semi-logarithmic plot of 4–5 of the last concentrations ($t_{1/2} = 0.693/k$). The area under the plasma drug concentration-time curve extrapolated to infinity (AUC) was calculated using the trapezoidal rule with extrapolation from the last observed concentration using $C(\text{last})/k$. Peak plasma drug concentrations (C_{max}) and the times of their occurrence (t_{max}) were determined directly from the data.

The milk/plasma (M/P) ratio of the drug was calculated in two ways, using mean AUC values for milk and plasma and the mean of paired milk and plasma drug concentrations after assumed equilibration between milk and plasma (i.e. excluding any detectable concentrations in the first hour after administration). The average milk concentration (C_{m}) was calculated from

Figure 1 Milk (○) and plasma (●) concentrations of zopiclone in 12 women after a 7.5 mg oral dose (mean $\pm$ s.d.)

$$\frac{\text{AUC}(0,22)}{22}$$

where 22 was the interval in hours between administration of the dose and lowest measurable drug concentration.

The relative dose ingested with breast milk was calculated from:

$$\frac{C_{\text{m}} \times 0.15 \times 60 \times 100}{D} \%$$

where 0.15 (kg^{-1}) was assumed to be the daily milk intake for a baby, 60 (kg) is the maternal body weight and D (mg) is the maternal dose.

Pharmacokinetic parameters after both types of delivery were compared using Student's unpaired *t*-test, those in milk and plasma were compared using the paired *t*-test. *P*-values below 0.05 were considered significant. The Kruskal-Wallis test was used to analyse whether the variation between individuals in mean ratios of paired milk and plasma concentrations was greater than that within individuals.

Results

Mean milk and plasma drug concentration vs time curves are shown in Figure 1. Pharmacokinetic parameters describing the time-course of drug in plasma and milk are shown in Tables 1 and 2. The time to peak in milk occurred significantly later than that in plasma. The elimination half-life was not significantly different in milk and plasma. Pharmacokinetic parameters did not differ significantly between women having Caesarean and those having vaginal delivery.

Table 1 Peak concentrations (C_{max}), time to peak (t_{max}), area under the curve (AUC) and elimination half life ($t_{1/2}$) of zopiclone in plasma and milk from 12 lactating women

Subject	Age (years)	Plasma				Milk			
		C_{max} ($\mu\text{g l}^{-1}$)	t_{max} (h)	AUC ($\mu\text{g l}^{-1} \text{ h}$)	$t_{1/2}$ (h)	C_{max} ($\mu\text{g l}^{-1}$)	t_{max} (h)	AUC ($\mu\text{g l}^{-1} \text{ h}$)	$t_{1/2}$ (h)
1	28	57	2	473	4.1	24	3	197	5.5
2	28	86	0.5	532	4.7	34	1	247	4.3
3	27	81	1	578	4.1	43	2	226	3.5
5	27	75	2	665	5.7	30	2	268	5.8
6	32	102	1	642	5.6	48	2	404	6.3
7	29	52	1	321	4.0	30	2	180	4.2
4	20	165	0.5	767	5.9	57	1	383	5.6
8	34	50	2	364	5.7	23	3	213	6.2
9	38	97	1	405	3.9	28	2	238	8.6
10	45	58	4	497	4.7	24	6	224	3.9
11	34	72	2	380	4.9	31	2	178	3.9
12	38	77	2	617	5.2	38	3	388	5.9
Mean	32	80	1.6	520	4.9	34	2.4	262	5.3
s.d.	7	32	1.0	138	0.7	11	1.3	84	1.4

Table 2 Milk/plasma ratio (AUC_m/AUC) of zopiclone, mode of delivery, days since delivery and serum albumin in 12 women given 7.5 mg zopiclone

Subject	Mode of delivery	Days since delivery	Serum albumin (g l^{-1})	AUC_m/AUC
1	vaginal	4	24	0.42
2	vaginal	3	28	0.46
3	vaginal	3	29	0.39
5	vaginal	2	28	0.40
6	vaginal	3	27	0.63
7	vaginal	3	31	0.56
4	*C-section	4	26	0.51
8	C-section	5	30	0.58
9	C-section	6	32	0.59
10	C-section	4	22	0.45
11	C-section	5	31	0.47
12	C-section	4	26	0.63
Mean		3.8	27.8	0.51
s.d.		1.1	3.0	0.09

*C = Caesarian

The mean ratio of paired milk and plasma concentrations showed significant ($P < 0.005$) interindividual variation (0.41–0.70), but no relationship to factors such as mode of delivery, days since delivery or lowered serum albumin concentration was observed in this small group of women.

The M/P-ratios based on paired concentrations were plotted against the M/P-ratios based on areas under the curve for each mother. A straight line was fitted to the points ($y = 0.8x + 0.06$, $r = 0.937$).

When the mean ratio of corresponding milk and plasma drug concentrations was plotted against time, a plateau was reached at 2 h after drug administration (Figure 2).

All mothers fell asleep, but they could be aroused easily for each sampling session. No adverse reactions were reported, although one mother had a depressive reaction which was possibly related to the drug or study procedure. All mothers were cooperative, but some of them subsequently complained about the comprehensive sampling procedure. The results of

Figure 2 Mean ($\pm$ s.d.) ratio of corresponding mean milk and plasma concentrations of zopiclone as a function of time after a 7.5 mg dose to 12 women.

haematological and biochemical tests were normal.

Assuming 100% drug absorption in the infant and a C_m of $11 \mu\text{g l}^{-1}$, the average dose of zopiclone in milk was calculated to be 1.4% of the weight adjusted dose ingested by the mother. The amount of zopiclone received by an infant was also calculated as the amount excreted in one feed (25 ml kg^{-1}) at 3, 7, 11, 15, 19 and 23 h after dosing. This corresponded to $1.5 \mu\text{g kg}^{-1}$ or 1.2% of the maternal dose. Nothing unusual was observed in the newborn infants during the study period.

Discussion

Most weak acids and bases diffuse into milk in their unbound, unionized forms to achieve total concentrations that depend on the pH-gradient between plasma and milk, the relative extent of protein binding in the two fluids and the partition coefficient.

As shown in Figure 2 the M/P ratio varied with time, but appeared to be constant after 2 h, when concentrations of zopiclone in milk were about half of those in plasma.

Delayed lactogenesis is reported in women having Caesarean sections (Neville, 1983). However, no difference in M/P values was observed between the mothers undergoing normal delivery and those who had Caesarean sections. Only large differences would be detected because a small number of mothers were studied and many biochemical changes take place during the early puerperium (Notarianni, 1990). Moreover, mothers having a Caesarian delivery were studied at a later stage, on average 4.7 vs 3.0 days after delivery. It is noteworthy that Gaillot

et al. (1983) found a M/P ratio of 0.6 in preliminary studies of three lactating mothers in the maternity ward.

Wilson *et al.* (1985) advocated calculation of the M/P ratio based on AUC values as an index of drug transfer to milk. In this study a good correlation was found between individual AUC_m/AUC values and the mean ratio based on paired sampling after equilibration was obtained at 2 h.

The kinetics of drugs may be different during labour and in the immediate postpartum period (Cummings, 1983). However, in general, pharmacokinetic parameters of zopiclone in our patients were comparable with those reported in non-pregnant women (Gaillot *et al.*, 1983; Houghton *et al.*, 1985), except that C_{max} was slightly higher (80 ± 32 and $64 \pm 19 \mu\text{g l}^{-1}$), even though the women in our study swallowed the drug in the supine position, which is reported to delay absorption (Channer *et al.*, 1984) and oral drug clearance ($\text{FD}/\text{AUC} = 0.75 \times 7.5/520 \times 60 \text{ ml} \times \text{min}^{-1} = 180 \text{ ml min}^{-1}$) was slightly lower than previously reported (230 ml min^{-1}).

Concerning the study design a less intensive sampling schedule might have been desirable considering the disturbance of sleep that it caused. It is emphasized that only mothers with established milk production and in apparently good physical and mental condition were selected.

The dose of a drug received by the breast-fed infant depends upon many factors including the number of consecutive doses to the mother, the time of feeding in relation to dosing, and the amount of milk fed. This study has demonstrated that the amount of zopiclone in breast milk is minimal after a single dose to the mother. Previous studies found no significant accumulation of zopiclone in plasma after 14 daily doses (Houghton *et al.*, 1985) and no active metabolites with long half-lives are known. The short half-life of zopiclone in milk suggests that there would be little accumulation of zopiclone in milk during regular daily dosing. However, the hepatic and renal elimination of zopiclone in the infant has not been investigated. Thus, we conclude that zopiclone, if prescribed to breast-feeding mothers, may be used on a short-term basis.

The authors are grateful to Kari Vegdahl for the skilful collection of milk samples. We also thank all the mothers who volunteered for the study. The study was supported by a Grant-In-Aid from Rhone Poulenc, France.

References

- Channer, K. S., Dent, M. K. & Roberts, J. C. (1984). The effect of posture at the time of administration on the central depressant effects of the new hypnotic zopiclone. *Br. J. clin. Pharmacol.*, **18**, 879–886.
- Cummings, A. J. (1983). A survey of pharmacokinetic data from pregnant women. *Clin. Pharmacokin.*, **8**, 344–354.
- Gaillot, J., Heusse, D., Houghton, G. W., Aurele, J. M. & Dreyfus, J. F. (1983). Pharmacokinetics and metabolism of zopiclone. *Pharmacology*, **27**, suppl. 2, 76–91.
- Goa, K. L. & Heel, R. C. (1986). Zopiclone. *Drugs*, **32**, 48–65.
- Houghton, G. W., Dennis, M. J., Templeton, R. & Martin, B. K. (1985). A repeated dose pharmacokinetic study of a new hypnotic agent, zopiclone Imovane®. *Int. J. clin. Pharmac. Ther. Tox.*, **23**, 97–100.
- Matheson, I. (1985). Survey of drug routines in Norwegian maternity wards. *Tidsskr. Nor. Lægeforen.*, **105**, 2281–2284.
- Matheson, I. (1989). Drugs to mother and infant in the maternity ward. A survey of five university hospitals in Norway. *Tidsskr. Nor. Lægeforen.*, **109**, 2118–2122.
- Neville, M. C. (1983). Regulation of mammary development and lactation. In: *Lactation. Physiology, nutrition and breast-feeding*, eds Neville, M. C. & Neifert, M. R., pp 104–140. New York: Plenum Press.
- Notarianni, L. (1990). Plasma protein binding of drugs in pregnancy and in neonates. *Clin. Pharmacokin.*, **18**, 20–36.
- Passmore, C. M., McElnay, J. D. & D'Arcy, P. F. (1984). Drugs taken by mothers in the puerperium: in-patient survey in Northern Ireland. *Br. med. J.*, **289**, 1593–6.
- Wickstrøm, E. & Giercksky, K.-E. (1980). Comparative study of zopiclone, a novel hypnotic, and three benzodiazepines. *Eur. J. clin. Pharmacol.*, **17**, 93–99.
- Wilson, J. T., Brown, R. D., Hinson, J. L. & Dailey, J. W. (1985). Pharmacokinetic pitfalls in the estimation of the breast milk/plasma ratio for drugs. *Ann. Rev. Pharmac. Tox.*, **25**, 667–689.

(Received 23 January 1990,
accepted 28 March 1990)