Br. J. clin. Pharmac. (1988), **26**, 45–51

Metronidazole excretion in human milk and its effect on the suckling neonate

C. M. PASSMORE, J. C. McELNAY, E. A. RAINEY[1] & P. F. D'ARCY
Pharmacy Practice Research Group, Department of Pharmacy, The Queen's University of Belfast, Medical Biology Centre, 97 Lisburn Road, Belfast, BT9 7BL and [1]Northern Ireland College of Midwifery, Royal Maternity Hospital, Grosvenor Road, Belfast BT12, Northern Ireland

1 Milk and plasma metronidazole and hydroxymetronidazole concentrations were measured in 12 breast-feeding patients following multiple doses of metronidazole (400 mg three times daily). All patients received metronidazole in combination with other broad spectrum antibiotics.
2 Plasma concentrations of both parent drug and metabolite were measured in seven suckling infants. Thirty-five infants were monitored for adverse reactions to maternal metronidazole therapy and two further groups of suckling infants, those whose mothers received either ampicillin alone or no drug therapy, were recruited as controls.
3 The mean milk to plasma ratio (M/P) was 0.9 for metronidazole and 0.76 for hydroxymetronidazole while the mean milk metronidazole concentrations (around C_{max}) were 15.5 $\mu g\ ml^{-1}$. The mean milk hydroxymetronidazole concentration was 5.7 $\mu g\ ml^{-1}$.
4 Infant plasma metronidazole concentrations ranged from 1.27 $\mu g\ ml^{-1}$ to 2.41 $\mu g\ ml^{-1}$, and the corresponding hydroxymetronidazole concentrations from 1.1 to 2.4 $\mu g\ ml^{-1}$.
5 There were no significant increases in adverse effects in infants which could be attributable to maternal metronidazole therapy.
6 Metronidazole was excreted in milk at concentrations which caused no serious reactions in the infants studied. The drug may therefore be administered at doses of 400 mg three times daily to mothers wishing to breast-feed their infants.

Keywords metronidazole neonate human milk

Introduction

During recent years there has been increased research into drug excretion in human milk, in particular with a number of recently introduced drugs e.g. aztreonam, captopril, diltiazem and tinidazole (Devlin & Fleiss, 1981; Evaldson *et al.*, 1985; Fleiss *et al.*, 1985; Okada *et al.*, 1985). These studies have concentrated on drug kinetics and while this is a very important aspect, previous studies have given little information about infant wellbeing and few studies have carried out specific infant monitoring protocols (e.g. Orme *et al.*, 1977; Notarianni, *et al.*, 1986). As a result there is insufficient information on the incidence of drug induced side-effects in the suckling infant (Fehrenbach, 1987).

Maternal antimicrobials are often required in the postnatal period and a prescribing survey in Northern Ireland showed that 4% of puerperal mothers received metronidazole therapy (Passmore *et al.*, 1983). Review and advisory publications (e.g. D'Arcy & McElnay, 1986; British National Formulary, 1987) recommend caution-

Correspondence: Dr J. C. McElnay, Pharmacy Practice Research Group, Department of Pharmacy, The Queen's University of Belfast, Medical Biology Centre, 97 Lisburn Road, Belfast BT9 7BL, Northern Ireland

ary use of metronidazole if required by breast-feeding mothers.

Metronidazole is used in the post-natal period for the treatment and prophylaxis of infection following Caesarian section, post-partum haemorrhage and other complications of childbirth in which infection is a possible hazard. The major plasma metabolite of metronidazole, hydroxymetronidazole, also has antimicrobial activity which may add to the potency of the parent drug (Finegold & Mathisen, 1985) and subsequently to any adverse reactions to metronidazole. Adverse reactions and minor side effects associated with short-term metronidazole therapy include nausea and gastrointestinal upsets, bad taste, furring of the tongue, dizziness, lethargy and minor skin rashes (Catterall, 1977; British National Formulary, 1987). Any of these adverse effects may occur in infants following the ingestion of metronidazole in milk including gastrointestinal effects, such as loose stools, candidiasis (both oral and perianal), and perhaps feeding difficulties due to the tainting of milk taste (British National Formulary, 1987; Golightly & Grant, 1985).

In our earlier survey (Passmore *et al.*, 1983), it was shown that metronidazole therapy was always given in combination with another broad spectrum antibiotic, such as a penicillin or a cephalosporin. Ampicillin was most commonly prescribed in this combination. It is therefore important that any infant monitoring studies carried out with metronidazole include recruitment of groups of control infants whose mothers receive ampicillin alone as well as those who receive no antimicrobial therapy.

Several groups of workers have previously investigated the excretion of metronidazole in human milk (Gray *et al.*, 1961; Moore & Collier, 1979; Erickson *et al.*, 1981; Heisterberg & Branebjerg, 1983). This present study was, however, specifically designed to monitor the metronidazole and hydroxymetronidazole (metabolite) concentrations in maternal milk and plasma over several dosing periods (under maternal steady-state conditions), to determine infant plasma concentrations and to monitor infants for adverse reactions to maternal metronidazole therapy.

Methods

Written, informed consent was obtained from mothers before they and/or their infants were recruited into the studies. The research project was approved by the Ethics Committee, Faculty of Medicine, The Queen's University of Belfast.

Milk and plasma sampling regimen

Twelve breast-feeding mothers, who were receiving metronidazole (400 mg three times daily) as part of their antimicrobial therapy were recruited to the study. Breast-feeding was well established in all mothers with sampling commencing 4.3 (± 0.4 s.e. mean) days post-partum. Milk samples were obtained by manual expression at 2, 4, 6 and 8 h and blood samples at 1, 2, and 8 h post dosing on the third and fourth days of treatments. None of the mothers was in the process of feeding at any of the sampling times. A blood sample (heelprick) was also taken from seven of their suckling infants on the fourth day of maternal treatment.

Assay of metronidazole and hydroxymetronidazole in milk and plasma

The assay method was an adaptation of the h.p.l.c. assay of Hackett & Dusci (1979). Maternal plasma samples (1 ml) were prepared for chromatographic analysis by precipation of proteins with acetonitrile (2 ml). Milk samples (1 ml) were skimmed before protein precipitation. Skimming did not interfere with drug recovery during sample preparation. The supernatants (1 ml) were evaporated to dryness under nitrogen, the residues were reconstituted with 1 ml of the chromatographic mobile phase and 100 μl injected onto the chromatographic column. Chromatography was performed using a μBondapak® 30 cm (3.9 mm i.d.) column with detection at 310 nm using a Spectroflow 773 variable wavelength detector. The chromatographic mobile phase, 7% v/v pH 4 acetate buffer in acetonitrile was used at a flow rate of 2 ml min^{-1}. Milk and plasma samples were analysed for metronidazole and hydroxymetronidazole concentrations with tinidazole (50 μg ml^{-1} of sample) as the internal standard. Aliquots of 0.2 ml of infant plasma were analysed for metronidazole and hydroxymetronidazole content. The mean milk metronidazole and hydroxymetronidazole concentrations obtained at each time point on the two sampling days were compared using paired *t*-tests. The milk: plasma ratios (M/P) calculated at all the relevant time points were similarly compared.

Infant monitoring for adverse reactions to maternal metronidazole

Three groups of infants were recruited to this section of the study; 35 whose mothers received metronidazole (two mothers concurrently received erythromycin, the remainder received

ampicillin of whom one changed to erythromycin and one to cephalexin within a few days of commencing ampicillin therapy), 24 whose mothers received ampicillin alone and 39 infants whose mothers received no antimicrobial therapy. Infants did not differ between groups with respect to birth weight or gestational age.

Monitoring record sheets were drawn up to allow standardisation of the reporting of possible adverse effects to maternal drug therapy. These were completed by paediatricians who were unaware of the infants' status within the study. The infants were monitored daily for up to the 10 days of maternal treatment for symptoms including furring of the tongue, napkin rash, the incidence of diarrhoea (or frequency of abnormally loose stools) and feeding difficulties. Buccal and perianal swabs to identify candidal overgrowth were also taken from infants and weight changes were documented. The results obtained for the three treatment groups (metronidazole combinations; ampicillin alone; and no maternal drug therapy) were compared using Fisher's exact test and analysis of variance (where appropriate).

Results

Metronidazole and hydroxymetronidazole were detected in all of the maternal milk, maternal plasma and infant plasma samples. The assay method was sensitive and specific with coefficient of variance values of 0.018 and 0.022 for metronidazole and hydroxymetronidazole, respectively, in milk (at concentrations of 10 $\mu g\ ml^{-1}$; $n = 10$) and 0.023 and 0.030, respectively, in plasma (10 $\mu g\ ml^{-1}$; $n = 10$).

Maternal milk and plasma metronidazole and hydroxymetronidazole concentrations are given in Table 1 while the infant plasma concentrations are presented in Table 2. The mean 2 h paired milk and plasma metronidazole concentrations over the 2 days were 15.52 $\mu g\ ml^{-1}$ and 17.46 $\mu g\ ml^{-1}$, respectively. The corresponding trough (8 h) milk and plasma concentrations were 9.07 $\mu g\ ml^{-1}$ and 9.87 $\mu g\ ml^{-1}$. The mean ($\pm$ s.e. mean) M/P over the two treatment days was 0.91 ± 0.2 (range: 0.59–1.36) for metronidazole and 0.77 ± 0.22 (range: 0.37–1.44) for hydroxymetronidazole. Using the paired *t*-test no significant difference was shown between the milk metronidazole and hydroxymetronidazole concentrations at each time point on the two sampling days. Furthermore the M/P at all points where paired samples were taken did not differ significantly. Table 2 includes the mean maternal milk metronidazole and hydroxymetronidazole concentration for each individual mother determined using all the milk sampling points. There was no correlation between the mean milk levels and the infant plasma metronidazole concentrations. The mean infant plasma metronidazole and hydroxymetronidazole concentrations were 1.62 $\mu g\ ml^{-1}$ and 1.42 $\mu g\ ml^{-1}$, respectively.

The infant monitoring results obtained are summarised in Table 3. There was no significant difference using Fisher's exact test between the results obtained for any of the monitoring tests performed. Anecdotal data obtained showed that two infants whose mothers received intravenous metronidazole and ampicillin had very loose stools which settled when the mothers commenced oral therapy. A further infant in the metronidazole group had firmer stools when the mothers concurrent therapy was changed from ampicillin to erythromycin. One infant in the ampicillin group had very loose stools accompanied by slight rectal bleeding, which settled when the maternal therapy was completed. Oral candidiasis was reported in one infant whose mother received the metronidazole/ampicillin combination therapy. This infant was treated with nystatin and the maternal drug therapy was suspended; the mother did not have any monilial infection. The fungal species was also isolated from the buccal and perianal swabs taken from an infant in the ampicillin control group with napkin rash. Although *Candida* species were isolated more often from infants in the metronidazole group than the non-drug group, and the growth obtained was consistently heavier than in the other two groups, this increase did not reach statistical significance ($P = 0.053$; Fisher's exact test).

No significantly increased weight loss was associated with maternal metronidazole therapy when the weight changes from birth to discharge in all groups were compared ($P > 0.05$; analysis of variance). No other abnormal signs in the infants were attributed to maternal metronidazole or ampicillin therapy.

Discussion

The M/P for metronidazole approached unity as has been shown previously by other groups of workers (Gray *et al.*, 1961; Heisterberg & Branebjerg, 1983). This present study has also shown that this ratio does not differ at the peaks and troughs of the dosing period. It also shows that, at steady-state, metronidazole and hydroxymetronidazole do not accumulate in milk from one day to the next. The M/P for hydroxymetronidazole (0.77) was lower than the parent drug (0.91) reflecting the more polar nature of the

Table 1 Mean (± s.e. mean; $n = 12$) steady state metronidazole (and hydroxy-metronidazole) concentrations ($\mu g\ ml^{-1}$) in milk and plasma of breast-feeding mothers on days 3 and 4 of metronidazole therapy (400 mg three times daily).

		Time post-dose (h)				
Day	*Sample*	*1*	*2*	*4*	*6*	*8*
	Milk	–	15.52	12.90	10.60	9.02
		–	±0.69	±0.59	±0.73	±0.59
		–	(5.73	(5.69	(5.62	(5.46
		–	±0.45)	±0.49)	±0.48)	±0.44)
3	Plasma	18.60	17.31	–	–	9.35
		±1.4	±0.96	–	–	±0.70
		(7.86	(7.03	–	–	(6.46
		±0.76)	±0.72)	–	–	±0.61)
	M/P*	–	0.91	–	–	0.96
		–	±0.03	–	–	±0.04
		–	(0.81	–	–	(0.84
		–	±0.07)	–	–	±0.07)
	Milk		15.52	12.8	10.57	8.99
			±0.73	±0.7	±0.64	±0.50
		–	(5.99	(5.96	(5.77	(5.47
		–	±0.44)	±0.44)	±0.39)	±0.35)
4	Plasma	14.9	17.6	–	–	10.46
		±1.3	±0.91	–	–	±0.76
		(7.46	(7.95	–	–	(7.23
		±0.81)	±0.60)	–	–	±0.46)
	M/P*	–	0.91	–	–	0.88
		–	±0.04	–	–	±0.04
		–	(0.75	–	–	(0.75
		–	±0.05)	–	–	±0.05)
	Milk	–	15.52	12.88	10.59	9.07
Mean		–	±0.52	±0.47	±0.47	±0.38
of		–	(5.47	(5.70	(5.63	(5.46
2		–	±0.34)	±0.34)	±0.33)	±0.29)
days						
	Plasma	16.73	17.46	–	–	9.87
		±1.02	±0.82	–	–	±0.52
		(7.47	(7.48	–	–	(6.84
		±0.54)	±0.49)	–	–	±0.39)

* M/P – Milk to plasma concentration ratio

metabolite. The two and three fold differences noted in the M/P for metronidazole and hydroxy-metronidazole respectively are also consistent with previously published data. The milk: plasma ratio is usually taken to be a constant for a particular drug molecule, however, the amount of drug excreted in milk is dependent on a number of factors such as the lipophilicity of the drug and its molecular weight, the pH of milk and plasma, fat content of milk and binding of the drug to proteins in milk and plasma. Individual differences and diurnal changes in any of these latter factors will therefore result in variations in the observed M/P. *In vitro* studies performed by Meskin & Lein (1985) have shown that the unionised/ionised ratio of basic drugs (such as metronidazole) is more important than lipophilicity in dictating the drug's M/P and thus variations in the pH of milk and plasma will be reflected in the concentrations detected in milk. The results presented in this study, therefore, serve to highlight the necessity for multiple subject and multiple sampling protocols when investigating the passage of any drug into milk.

Assuming a total daily intake of 500 ml of milk, the mean amount of metronidazole ingested daily by the suckling neonate would be 6.25 mg. This is less than 10% of the recommended daily dose for infants of equivalent age and weight (7.5–15 mg kg^{-1} 8 h^{-1}; approximately 67.5 mg–

Table 2 Plasma metronidazole (and hydroxymetronidazole) concentrations in seven breast-fed infants following maternal metronidazole administration.

Maternal milk concentration[1] *(mean; μg ml*$^{-1}$*)*	*Infant plasma concentration (μg ml*$^{-1}$*)*	*Infant sampling time (h)*[2]	*Feeding/ sampling interval (min)*[3]
10.67 (3.65)	1.51 (1.10)	4	not available
15.22 (8.53)	2.41 (2.40)	7	30
12.96 (4.53)	1.41 (1.26)	7	45
14.20 (6.30)	1.27 (1.30)	7	45
14.29 (4.48)	1.47 (1.67)	8	30
11.25 (7.38)	2.1 (1.20)	7	not available
12.04 (4.01)	1.15 (1.03)	8	90
Mean (± s.e. mean) metronidazole			
12.95 ±0.64	1.62 ±0.17	6.85 ±0.51	48.0 ±11.0
Mean (± s.e. mean) hydroxymetronidazole			
5.55 ±0.71	1.42 ±0.18	6.85 ±0.51	48.0 ±11.0

1 Mean of milk concentrations determined throughout the two dosing periods.
2 Time post maternal dosing when infant sample was obtained.
3 Time lapse between infant feed and blood sampling.

135 mg daily) and the plasma concentrations were again less than a tenth of the concentrations achieved following therapeutic doses (Jager-Roman *et al.*, 1982; Amon *et al.*, 1983).

The results obtained in the monitoring studies were anecdotal with slight, but not significant, increases in the incidence of loose stools and in the isolation of *Candida* species in infants whose mothers received the metronidazole combination. The frequency and texture of these loose stools were not severe enough to be diagnosed as diarrhoea and no apparent discomfort was recorded in any of the infants studied. None of the infants had any clinical indications to corroborate the case report (Clements, 1980) of secondary lactose intolerance induced by metronidazole ingested in milk. The single case of oral candidiasis, and the increase in species isolation in infants whose mothers received metronidazole suggests an associated risk. While these two reported reactions may occur slightly more often in the newborn infant whose mother receives metronidazole combination therapy and may cause distress and concern to mothers, our evidence suggests that they can be alleviated by the temporary suspension of either breast-feeding or maternal therapy.

Although the minor reactions reported were more frequent in the metronidazole combination group than in the ampicillin group, there was some evidence in the present study to show that ampicillin alone may adversely affect the suckling infant. It is therefore suggested that the excretion of ampicillin in human milk and its effect on the suckling infant warrants further study.

The most serious reason for contraindicating metronidazole therapy for breast-feeding mothers may be the risk to the infant due to the mutagenic activity of the drug referred to by Heisterberg & Branebjerg (1983). There is debate about the carcinogenic potential of metronidazole in mammalian cells (Roe, 1983). We

Table 3 Infant monitoring data for breast-fed infants whose mothers received combined metronidazole therapy, ampicillin only or no drug therapy.

Reaction		*Infant group* *Metronidazole combination*	*Ampicillin only*	*Control*
Number of infants with changes in stool consistency		1 constipated 2 loose 3 very loose	1 constipated 2 loose 1 very loose	1 very loose
Number of infants with napkin rash		1	0	1
Number of infants with feeding problems		4	4 (2 stopped breast feeding)	2
Mean (± s.e. mean) changes in infant weight from birth to hospital discharge. (g)	(a)	+7.6 (±32.0)	−126.0 (±24.3)	−85.5 (±17.1)
	(b)	−36 (±32.1)	−46.0 (±27.2)	−69.8 (±44.7)
Number of infants from whom *Candida* species were isolated	(c)	1	2	0
	(d)	6	3	3
Number of infants sampled		24	18	31

(a) – Infants weighed 4–6 days post-partum
(b) – Infants weighed 7–9 days post-partum
(c) – buccal swabs
(d) – perianal swabs

have recently considered this problem and have shown that metronidazole is weakly mutagenic to mouse lymphoma cells (unpublished data). It has been suggested that hydroxymetronidazole may present a greater risk of mutagenic change (Heisterberg & Branebjerg, 1983). However, our most recent work does not support this finding. In conclusion this very weak mutagenic potential, especially at drug concentrations found in milk, the lack of evidence to link metronidazole to human carcinogenicity (Beard *et al.*, 1979), and the low incidence of adverse reactions noted in the present study, suggests that metronidazole may be safely administered to mothers at oral doses of 400 mg three times daily.

We wish to thank the medical and nursing staff of the Jubilee Maternity Hospital and the Royal Maternity Hospital, Belfast and Miss Mary Graham, N. I. College of Midwifery for their help with this study. Financial support for the work was obtained from The Wellcome Trust and the Department of Health and Social Services, Northern Ireland.

References

Amon, I., Amon, K., Scharp, H., Franke, G. & Nagel, F. (1983). Disposition kinetics of metronidazole in children. *Eur. J. clin. Pharmac.*, **24**, 113–119.

Beard, M. C., Noller, K. L., O'Fallon, W. M., Kutland, L. T. & Dockerty, M. B. (1979). Lack of evidence of cancer due to use of metronidazole. *New Engl. J. Med.*, **301**, 519–521.

British National Formulary (1987). *Prescribing during breast-feeding*. British National Formula, No 14. London: British Medical Association, The Pharmaceutical Society of Great Britain.

Catterall, R. D. (1977). Fifteen years experience with metronidazole. In: *Metronidazole, Proceedings of the international metronidazole conference*, Montreal, eds Finegold, S. M., McFadzean, J. A. & Roe, F. J. C., pp. 107–111. Princeton N.J: Excerpta Medica.

Clements, C. J. (1980). Metronidazole and breast feeding. *N. Z. med. J.*, **92**, 329.

D'Arcy, P. F. & McElnay, J. C. (1986). Drugs in milk. In *Iatrogenic diseases*, third edition, eds D'Arcy, P. F. & Griffin, J. P., pp. 479–512, Oxford: Oxford University Press.

Devlin, R. G. & Fleiss, P. M. (1981). Captopril in human blood and breast milk. *J. clin. Pharmac.*, **21**, 393–396.

Erickson, S. H., Oppenheim, G. L. & Smith, G. M. (1981). Metronidazole in breast milk. *Obstet. Gynaecol.*, **57**, 48–50.

Evaldson, G. R., Lindgren, S., Nord, C. E. & Rane, A. T. (1985). Tinidazole milk excretion and pharmacokinetics in lactating women. *Br. J. clin. Pharmac.*, **19**, 503–507.

Fehrenbach, A. (1987). Drugs in breast milk. *Br. J. pharm. Prac.*, **9**, 288–297.

Finegold, S. M. & Mathisen, G. E. (1985). The treatment of anaerobic bacterial infections. In *Current clinical topics in infectious diseases 6*. eds Remington, J. S. & Swartz, M. N., pp. 156–196. New York: McGraw-Hill.

Fleiss, P. M., Richwald, G. A., Gordon, J., Stern, M., Franz, M. & Devlin, R. G. (1985). Aztreonam in human serum and breast milk. *Br. J. clin. Pharmac.*, **19**, 509–511.

Golightly, P. E. & Grant, E. (1985). Breast feeding and drug therapy 2: Problem areas. *Pharmacy International*, **6**, 279–284.

Gray, M. S., Kane, P. O. & Squibb, S. (1961). Further observations on metronidazole in breast milk. *Br. J. Vener. Dis.*, **37**, 278–279.

Hackett, L. P. & Dusci, L. J. (1979). Determination of metronidazole and tinidazole in human plasma. *J. Chromatogr.*, **175**, 347–349.

Heisterberg, L. & Branebjerg, P. E. (1983). Blood and milk concentrations of metronidazole in mothers and infants. *J. perinat. Med.*, **11**, 114–120.

Jager-Roman, E., Doyle, P. E., Bart-Lambert, J., Cvejic, M. & Buchanan, W. (1982). Pharmacokinetics and tissue distribution of metronidazole in the newborn infant. *J. Pediatr.*, **100**, 651–654.

Meskin, M. S. & Lein, E. J. (1985). QSAR analysis of drug excretion into human breast milk. *J. clin. hosp. Pharm.*, **10**, 269–278.

Moore, B. & Collier, J. (1979). Drugs and breast feeding. *Br. med. J.*, **2**, 211.

Notarianni, L. J., Humphries, S. J., Ferrie, J. G., Marriot, B. A., Cain, A. R., Osborne, J., Reckless, J. & Bennett, P. N. (1986). Effect of carbimazole during lactation on the neonate. *Presented to the III World Conference of Clinical Pharmacology & Therapeutics, Stockholm, (Poster No. 519)*.

Orme, M. L'E., Lewis, P. S., De Swiet, M., Serlin, M. J., Sibeon, R., Baty, J. D. & Breckenridge, A. M. (1977). May mothers given warfarin breast feed? *Br. med. J.*, **1**, 1564–1565.

Okada, M., Inoue, H., Nakamura, Y., Kishimoto, M., Suzuki, T. (1985). Excretion of diltiazem in human milk. *New Engl. J. Med.*, **312**, 992–993.

Passmore, C. M., McElnay, J. C. & D'Arcy, P. F. (1983). Drugs taken by mothers in the puerperium: an inpatient survey in Northern Ireland. *Br. med. J.*, **289**, 1593–1596.

Roe, F. J. C. (1983). Toxicological evaluation of metronidazole with particular reference to carcinogenicity, mutagenicity and teratogenic potential. *Surgery*, **93**, 158–164.

(Received 12 November 1987, accepted 4 March 1988)