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Tinidazole milk excretion and pharmacokinetics in lactating women

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1 Five women undergoing acute Caesarean section were given an i.v. dose of 1600 mg tinidazole preoperatively as prophylaxis against anaerobic infection. Blood and breast milk samples were collected at 8 and 4 h intervals, respectively, for 120 h. Tinidazole concentrations were measured by means of high performance liquid chromatography (h.p.l.c.).

2 The concentration of tinidazole in breast milk was highly related to the concentration in serum ($r = 0.969$). Tinidazole concentrations in serum declined monoexponentially with an average half-life of 11.4 h (range 8.7–13.1). The milk/serum concentration ratio varied between 0.62 and 1.39. Seventy-two hours after the Caesarean section the milk concentration exceeded 0.5 μg/ml in only one woman. It may be calculated that at this time the maximum daily dose to the infant would be 0.1 mg/kg body weight (assuming 3.5 kg body weight and 400 ml milk consumed).

3 We conclude that until tinidazole has been proven harmless to the neonate breast feeding following i.v. administration of 1600 mg should not be initiated earlier than 72 h after the dose.

Keywords tinidazole breast milk pharmacokinetics

Introduction

The incidence of infectious complications following Caesarean section has been reported to be as high as 48 to 85 per cent (Gibbs *et al.*, 1978; de Palma *et al.*, 1980). It is significantly higher in emergency cases as compared with patients undergoing elective surgery (Hägglund *et al.*, 1983). The importance of prophylactic administration of antibiotics to these patients at risk has been unequivocally demonstrated (Polk, 1981).

Since anaerobic bacteria are often involved in these and other gynaecological diseases (Gilstrap & Cunningham, 1979; Middleton *et al.*, 1980; Dizerega *et al.*, 1980) nitroimidazoles have been suggested to be the drugs of choice in cases of emergency Caesarean section (Vaughan, 1979; Gerstner *et al.*, 1980). The efficacy of nitroimidazoles used prophylactically in these patients has been well documented (Vaughan, 1979; Gerstner *et al.*, 1980) as has the low frequency of side effects (Andersson, 1981). So far no adverse effects of nitroimidazoles have been demonstrated in neonates (Amon *et al.*, 1972). Nevertheless, the use of these drugs at Caesarean section necessitates studies of their pharmacokinetics in the mother as well as of the breast milk excretion. Whilst metronidazole pharmacokinetics and breast milk excretion have been studied (Erickson *et al.*, 1981; Heisterberg & Branebjerg, 1983), no reports on tinidazole from this respect seem to have been published. The scope of the present study was to investigate the excretion of tinidazole in the breast milk as well as its pharmacokinetics in the post partum women that received this drug at Caesarean section.

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Methods

Five women undergoing acute Caesarean section were included in the study. The study design had been approved by the local Ethics committee, and all patients had given their consent to participate. The clinical indications for the surgery are given in Table 1.

Intravenous infusion of 1600 mg tinidazole was started during surgery as soon as the umbilical cord had been clamped. The total dose was administered within 1.5 h. Postoperatively, serum samples were collected every 8 h. As soon as breast milk production started the milk was collected quantitatively every 4 h from the right and left breast separately. The milk samples were collected with the use of an electrical pump. The mothers were not allowed to breast-feed their babies until the concentrations of the drug had reached unmeasurable levels as determined by a rapid microbiological assay. An aliquot of 100 μl milk was used for determination of the tinidazole concentration by an agar diffusion method using *Clostridium sporogenes* strain 243 as an indicator strain. Bacto Penassay seed agar (Difco, Detroit, Michigan) was used as test medium. The use of this microbial determination of tinidazole in the breast milk made it possible with the shortest delay necessary to commence breast feeding at unmeasurable levels of the drug (the test results were available within 24 h). With the exception of the small amount of breast milk needed for the microbiological assay of tinidazole all breast milk and serum samples were immediately frozen at −70°C until analysis.

Chemical analysis of tinidazole in serum and breast milk was carried out at the Huntington Research Centre, Huntington, England, by means of high performance liquid chromatography (h.p.l.c.). In brief, h.p.l.c. was carried out with a PU 4010 pump and a PU 4020 variable wavelength UV detector (Pye Unicam Ltd, Cambridge). A reversed-phase system was used with a Spherisorb 5 ODS column. The lower limit of detection was 0.5 μg/ml.

The serum half-life ($t_{½}$) and the elimination rate constant (k_e) for tinidazole in serum were calculated by linear least squares regression analysis. The milk/serum concentration ratio of tinidazole was calculated as the mean of several simultaneous concentration data pairs in each patient. The systemic clearance of tinidazole (CL) was estimated from the following equation

$$CL = k_e \times V_d$$

in which V is the apparent volume of distribution. The V_d was obtained from the equation

$$V_d = \frac{\text{Dose}}{C_o}$$

where C_o is the serum concentration at zero time. The value for C_o was obtained by extrapolation to the ordinate of the regression line for the serum concentrations.

Results

The start of the milk production, the daily volumes produced during the first 96 h after surgery, as well as the total amounts of tinidazole excreted in the breast milk are displayed in Table 2. During the first 24 h after the infusion no or very little milk was produced. Nevertheless, in patients 2 and 3 significant amounts of tinidazole were excreted during the first day. There was a large interindividual variation in milk volumes and excreted drug. Thus, patient 1 was found to

Table 1 The clinical indications for surgery

Patient	*Maternal body weight (kg)*	*Child birth weight (g)*	*Cause of the Caesarian section*	*Concomitant drug treatment*
1	74	2570	Placental insufficiency + imminent asphyxia	—
2	64	1280	Premature breech presentation	ampicillin
3	87	3540	Premature rupture of the membranes + imminent asphyxia	—
4	77	3820	Postmaturity + imminent asphyxia	fenantoin (from day 1 postoperatively)
5	88	4730	Prolonged labour + 'macrosomia'	

excrete several fold larger amounts than all other women.

The excretion of tinidazole in breast milk was highly related to the serum concentration in each individual patient (Figure 1). The correlation coefficient (r) between the serum and breast milk concentrations varied between 0.994 and 0.999. There was little variation in the slope of these regression lines.

The kinetics of tinidazole in the women were linear with monoexponential decay and half-lives varying between 8.7 and 13.1 h (Table 3). The calculated clearance values are consistent with a low clearance drug and varied between 27 and 60 ml kg^{-1} body weight h^{-1}.

Discussion

Tinidazole is a young member of the nitroimidazole group of drugs and is frequently used in treatment of anaerobic infections. The present investigation was undertaken since tinidazole may be used as a prophylactic antibacterial agent in women subjected to acute Caesarean section. It was of major concern to study the excretion in breast milk in order to estimate when breast feeding may be started after an infusion of the drug at surgery.

All women displayed similar kinetics of the drug in serum and there was little interindividual variation. The values for the $t_{½}$ and V_d are consistent with values reported for non-pregnant, non-lactating women (Mattila *et al.*, 1983) and men (Charuel *et al.*, 1981).

The average milk/serum concentration ratio varied between 0.62 and 1.39 and was relatively constant during the study period. This indicates that the secretion into milk is not concentration dependent.

Low tinidazole milk concentrations (at the limit of sensitivity of the h.p.l.c. method) were reached 53 to 84 h after dose. At this time the levels were about 0.5 μg/ml. In one of the women (no. 1) the milk concentration was about 0.9 μg/l at 72 h. It may be calculated that, in this case, the daily dose to an infant would be about 0.1 μg/kg body weight (assuming a daily milk volume of 400 ml and a neonatal body weight of 3.5 kg). This estimate is made from the woman with the highest milk concentrations and milk volumes and therefore not representative for all included patients. Nevertheless, this value is considerably lower than the therapeutic single infusion dose (about 20 mg/kg) administered to the mothers. However, it is difficult to predict what levels of tinidazole will be achieved in a breast-fed infant since its metabolic and excretory processes may be compromised (Rane, 1980). A

Table 2 Daily volumes of breast milk produced and concentration of tinidazole excreted in breast milk

Patient	*Start of milk production (h post dosing)*	*Volume of breast milk produced (ml)*					*Total amount of tinidazole in breast milk (μg/ml)*				
		0–24	*25–48*	*49–72*	*73–96*	*0–96 h*	*0–24*	*25–48*	*49–72*	*73–96*	*0–96 h*
1	38	0	76	369	283	728	0	279.32	529.36	117.09	925.77
2	24	3	5	49	133	190	17.31	4.84	3.36	ND	25.51
3	22	2	2	49	121	174	27.70	5.72	52.87	7.28	93.57
4	33	0	17	72	128	217	0	13.77	39.54	ND	53.31
5	14	5	7	56	89	157	ND	5.31	27.66	ND	32.97

ND = not detected (< 0.05 μg/ml)

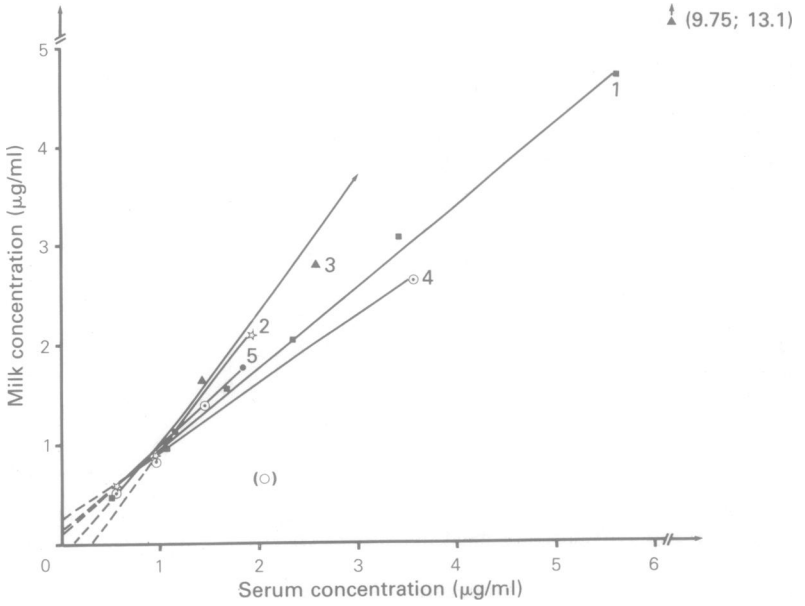

Figure 1 Tinidazole milk/serum concentration relationships in five lactating women.
The observation in patient no 4 marked (○) has been excluded from the calculation of the regression line.

Table 3 Tinidazole kinetics in the mothers

Patient	*i.v. dose (mg/kg)*	$t_{1/2}$ *(h)*	k_e (h^{-1})	V_d *(l/kg)*	*CL* $(ml\ kg^{-1}\ h^{-1})$	r^2	r
1	(1600/74) 21.62	13.09	0.0529	0.508	27	0.9976	0.9988
2	(1600/64) 25.00	8.72	0.0795	0.771	60	0.9994	0.9997
3	(1600/87) 18.39	11.72	0.0591	0.511	30.2	0.9974	0.9987
4	(1600/77) 20.78	11.98	0.0578	0.8846	51.1	0.9979	0.9990
5	(1600/88) 18.18	11.27	0.0615	0.6036	37.1	0.9983	0.9992

different approach may be taken if one considers how large a fraction of the maternal body content of drug that will be transferred daily to the infant at a given milk secretion rate. If one assumes a V_d of 1 l/kg and a daily milk volume of 0.5 l only 0.7 % of the maternal body content will be transferred to the baby (assuming a milk/serum concentration ratio of 1.0).

It is our opinion that breast feeding may start 3 days after prophylactic treatment with 1600 mg tinidazole i.v., the estimated exposure to tinidazole being considered minimal and probably neglectable.

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