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Excretion of indomethacin in breast milk

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1 The excretion of indomethacin into breast milk and subsequent exposure of infants was studied in 16 women and seven of their infants. The median milk:plasma ratio in seven patients where there were measurable drug concentrations in both milk and plasma was 0.37.

2 Total infant dose, assuming a daily milk intake of 150 ml kg^{-1} and 100% absorption, ranged from 0.07% to 0.98% (median = 0.18%) of the weight adjusted maternal dose.

3 Plasma samples were obtained in seven infants. In six of these, indomethacin concentrations were below the sensitivity of the assay (< 20 $\mu g\ l^{-1}$), while one infant had a plasma indomethacin concentration of 47 $\mu g\ l^{-1}$.

4 No adverse effects due to indomethacin were reported in the infants.

Keywords indomethacin milk infant relative maternal dose

Introduction

Indomethacin, a non-steroidal anti-inflammatory drug, is now widely used for its analgesic and anti-inflammatory properties following abdominal surgery, including caesarean section (Engel *et al.*, 1989; Thind & Sigsgaard, 1988). Use of indomethacin in women post-partum for pain relief has led to concern about its possible passage into breast milk and potential adverse effects in young infants. These concerns are based on a single case report of convulsions in a young breast fed infant whose mother was taking indomethacin (Eeg-Olofsson *et al.*, 1978). Despite the fact that no data on indomethacin concentration in maternal serum, breast milk or infant serum were provided in that report, it was concluded by the authors that the presence of indomethacin in breast milk was the cause of the convulsions.

However, a review of the physico-chemical properties of indomethacin suggests that it is unlikely to be concentrated in breast milk. The pKa of 4.5 (Hansch & Leo, 1979), sparing lipid solubility (log $P_{octanol:pH\ 7.4\ buffer}$ = −1; Hansch & Leo, 1979) and high plasma protein binding (> 90%; Helleberg, 1981) all mitigate against its transfer from the blood into milk.

In the present study we have measured the concentration of indomethacin in the milk of nursing mothers with the aim of producing data which will enable a rational assessment of the potential toxicity of the drug in the breast fed infant.

Methods

Patients

Sixteen breast feeding women were enrolled in the study. The women ranged in age between 18 and 37 years with pre-delivery body weights ranging from 56 to 102 kg. Indomethacin was prescribed for various conditions; pain associated with caesarean section (10), back pain (2), thrombophlebitis (2), prolapsed disc (1) and broken forearm (1). All patients had received indomethacin for at least 48 h prior to sampling, with daily doses ranging between 75 mg orally and 300 mg rectally. With one exception, the women were less than 10 days post partum. Patient (5) was 10 months post delivery and entered the study after contacting the Hospital Drug Information Service and requesting information on the passage of indomethacin into her breast milk. The design of the study was approved by the KEMH Ethics Committee and all patients gave written informed consent to their participation.

Several women were taking concomitant medication, none of which interfered in the assay procedures. Milk samples (10–20 ml) were collected both immediately before and after infant feeding using a manual breast pump. Blood samples were taken from the mothers at the same time. In seven cases, blood from the nursing infants was obtained for assay of indomethacin.

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Analytical methods

Indomethacin concentrations in plasma and milk were measured by h.p.l.c. For estimation in plasma, standards were prepared by adding known amounts of indomethacin to blank plasma, giving final concentrations in the range 25–300 μg l^{-1}. For milk samples, known amounts of indomethacin were added to the actual patient samples to give final concentrations in the range 25–150 μg l^{-1}. Plasma or milk (0.2 ml) was added dropwise to 0.2 ml acetonitrile containing flufenamic acid (4.8 mg l^{-1}) as the internal standard. The samples were then centrifuged at 1500 *g* for 3 min and a 0.2 ml aliquot of the protein free supernatant was transferred to a clean tube. Heptane (0.2 ml) was added, the contents were vortexed for 30 s, centrifuged as above and the heptane layer aspirated to waste. The acetonitrile layer was then evaporated to dryness at 60°C under a stream of dry N_2 and the residue reconstituted in 0.2 ml of h.p.l.c. mobile phase by vortexing and sonicating.

After a further centrifugation as above, 0.08 ml aliquots were subjected to h.p.l.c. analysis. A Beckman ODS 5 μ column (25 cm × 4.6 mm i.d.) with a Bio-Rad reversed phase Micro-Guard precolumn were used together with a mobile phase of 60% methanol in 33 mM phosphate buffer (pH 6). The solvent was pumped at 1 ml min^{-1} and eluting peaks were detected by monitoring their ultra-violet absorbance at 270 nm at a sensitivity of 0.01 aufs. Unknown concentrations of indomethacin in plasma were interpolated from a plasma standard curve run with each batch of assay samples, while concentrations in milk were determined from the y-intercept of a milk standard curve which had been produced by addition of known amounts of drug to individual patient samples. The coefficient of variation for the assay of indomethacin in plasma ranged from 3.1% at 89 μg l^{-1} to 0.82% at 4600 μg l^{-1} (n = 5).

Calculation of dosage

The absolute dose was calculated by taking the maximum concentration obtained in milk (or the sensitivity limit of the assay) and converting it to a mg kg^{-1} day^{-1} dose using an estimated infant milk consumption of 0.15 l kg^{-1} day^{-1} (Bennett, 1988). The relative dose of indomethacin received by a nursing infant was calculated as the absolute infant dose × 100 divided by the maternal dose, where both doses are expressed as mg kg^{-1} day^{-1} (Bennett, 1988).

Results

The daily indomethacin dose ingested, concentrations in maternal plasma and milk:plasma (M:P) ratios (where applicable) are shown in Table 1. In eight studies, measurable concentrations of indomethacin were found in the pre-feed (59 ± 13 μg l^{-1}; mean ± s.e. mean) and post-feed (69 ± 13 μg l^{-1}) milk samples. Analysis of these data by a paired t-test indicated that the pre- and post-feed concentrations were not significantly different (t = 1.31, P = 0.23). The milk concentrations shown in Table 1 have therefore been expressed as an average of the pre- and post-feed concentrations. The times after dose for the milk samples were calculated relative to the midpoint of the feed. Maternal daily dose varied from 0.94 to 4.29 mg kg^{-1} day^{-1} and was not correlated with measured concentrations of indomethacin in plasma (range 23–1965 μg l^{-1}) or milk (range 23–

Table 1 Indomethacin dose rate, concentrations in milk and maternal plasma and milk:plasma ratio

		Indomethacin				
		Time after dose (h)		*Concentration (μg l^{-1})*		
Patient[a] number	*Dose (mg kg^{-1} day^{-1})*	*Milk*	*Plasma*	*Milk*	*Plasma*	*Milk:plasma ratio*
1	0.94	2.2	2.5	23	318	0.07
2	0.96	3.5	3.8	<20	336	<0.06
3	1.10	6.7	6.8	<20	<20	–
4	1.43	6.5	6.8	115	313	0.37
	1.43	1.8	2.8	65	397	0.16
5	1.67	22.6	–	<20	–	–
	1.67	14.5	–	<20	–	–
6	1.70	4.5	5.3	<20	98	<0.20
7	1.75	6.8	6.5	<20	95	<0.21
8	2.50	2.0	3.6	<20	242	<0.08
	2.50	16.3	–	<20	–	–
9	2.67	21.4	19.8	<20	<20	–
10	2.78	3.0	3.3	<20	149	<0.13
11	2.86	11.5	12.0	<20	80	<0.25
12	2.86	–	17.5	34	23	1.48
13	2.94	2.3	2.9	111	1914	0.06
14	3.57	10.2	10.8	46	66	0.7
	3.57	15.8	–	36	–	–
15	4.26	2.5	3.4	81	187	0.43
16	4.29	0.7	0.8	<20	1965	<0.01

[a]Patients 4, 5, 8 and 14 were studied on two consecutive days.
– Indicates no data available.

Table 2 Demographic characteristics of the infants, their plasma indomethacin concentrations and dose exposure

Infant of patient	*Sex*	*Body weight (kg)*	*Time of plasma sample (h)*[a]	*Indomethacin plasma concentration ($\mu g\ l^{-1}$)*	*Absolute dose*[b] *($mg\ kg^{-1}\ day^{-1}$)*	*Relative dose in milk*[b] *(%)*
1	F	3.95	0.6	<20	0.004	0.43
2	F	2.91	–	–	<0.003	0.31
3	M	3.43	0.4	<20	<0.003	0.27
4	F	2.67	1.3	<20	0.014	0.98
5	F	10.00	–	–	<0.003	0.18
6	M	3.55	1.3	<20	<0.003	0.18
7	M	0.45	–	–	<0.003	0.17
8	F	4.16	–	–	<0.003	0.12
9	F	3.70	–	–	<0.003	0.11
10	M	3.45	–	–	<0.003	0.11
11	F	3.42	–	–	<0.003	0.11
12	M	3.06	–	–	0.005	0.18
13	F	2.65	1.2	47	0.017	0.58
14	F	2.24	0.7	<20	0.006	0.17
15	F	3.19	–	–	0.012	0.28
16	M	4.46	−2.7	<20	<0.003	0.07

[a]Times specified relative to mid-point of feed.
[b]Calculated as specified in methods.

111 $\mu g\ l^{-1}$). The median M:P ratio was 0.37 (range 0.06–1.48) in those studies with measurable indomethacin concentrations in both fluids ($n = 7$) and < 0.13 (range < 0.1–< 0.25) in those studies where indomethacin concentration in milk was below the detection limit ($n = 7$).

Table 2 summarizes the demographic characteristics of the infants, their plasma drug concentrations and total indomethacin dose exposure expressed as the absolute dose and as a percentage of the maternal dose. Plasma samples were only obtained from seven infants. Plasma indomethacin concentration was below the assay limit in six infants and present at 47 $\mu g\ l^{-1}$ in the seventh. Dose calculations for all 16 infants showed that absolute dose rate ranged from < 0.003–0.017 mg $kg^{-1}\ day^{-1}$ while relative dose in milk ranged from 0.11–0.98% (median = 0.18%).

Discussion

A previous report (Eeg-Olofsson *et al.*, 1978) implicated the ingestion of indomethacin, via breast milk, as the cause of seizures in a 7 day old infant. However, no samples of milk or serum were taken to confirm the exposure. Based on this single unconfirmed report some reviewers (McEvoy, 1990; Needs & Brooks, 1985) recommended that indomethacin should be avoided by women who are breast feeding.

Data from the present study show that indomethacin is excreted into milk in very small amounts. Daily maternal indomethacin doses ranging from 0.94 to 4.29 mg $kg^{-1}\ day^{-1}$ resulted in very low M:P ratios. Only one patient (12) recorded a high M:P ratio (1.48), although in this case, the actual milk (34 $\mu g\ l^{-1}$) and plasma (23 $\mu g\ l^{-1}$) indomethacin concentrations were very low and the time of milk sample collections could not be confirmed. The data showed also that indomethacin concentrations in pre- and post-feed milk samples were not significantly different and therefore not influenced by the increase in milk lipids which occurs during feeding (Wilson *et al.*, 1980). This finding confirms a recent *in vitro* study which showed that indomethacin binding to milk components at 37°C was 54.6% and 65.6% in milk with 0.75 and 3.5% fat content, respectively (Macheras *et al.*, 1990).

In adults, indomethacin undergoes *O*-demethylation and *N*-deacylation to inactive metabolites and only a small percentage of a dose is excreted unchanged in the urine (Helleberg, 1981). Total clearance in adults ranges from 44–109 ml $h^{-1}\ kg^{-1}$ (Alvan *et al.*, 1975). While the elimination pathways for indomethacin in neonates have not been studied, the much lower total clearance in this group (7.6 ± 3.0 ml $h^{-1}\ kg^{-1}$; Vert *et al.*, 1980) strongly suggests that neonatal metabolic pathways for the drug are immature. However, by 1 year of age total clearance of indomethacin has increased to around 192 ml $h^{-1}\ kg^{-1}$ (Olkkola *et al.*, 1989). Therefore, breast fed neonates have an increased potential to accumulate the indomethacin they receive from their mother's milk. Our data show that infants could ingest only relatively small amounts of indomethacin via breast milk. For example, the maximum absolute daily dose (0.017 mg $kg^{-1}\ day^{-1}$), corresponds to only 4.2–8.5% of the intravenous dose of indomethacin (0.2 mg kg^{-1} 12–24 hourly for three doses) used to treat patent ductus arteriosus (Walters, 1988). The total indomethacin dose exposure of the infants, calculated as the relative dose in milk was extremely low.

Actual exposure of the infant to drug may well be much less because absorption of orally administered indomethacin in the neonate has been shown to be slow and incomplete (Vert *et al.*, 1980). With one exception, infant serum drug concentrations were below the limit of the assay (< 20 $\mu g\ l^{-1}$). No drug related untoward effects were observed in any of the infants, either during their hospital stay or after discharge.

Most of our data were collected between 3 and 9 days after delivery and reflect indomethacin exposure during short term therapy. However, data from patient (5), who was taking indomethacin for a broken forearm and was still breast feeding 300 days after delivery, were similar to those obtained from patients during the first few days after delivery. Nevertheless, we would suggest that infants should still be closely monitored for possible adverse effects during maternal indomethacin therapy.

Our results show that only very small amounts of indomethacin pass into breast milk and subsequent exposure of the infant is minimal. Lactating women taking indomethacin in usual therapeutic doses, and who wish to breast feed, should not be discouraged from doing so.

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