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Metoclopramide and Breast Feeding: Transfer into Milk and the Newborn

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Summary. The pharmacokinetics and endocrinological effects of metoclopramide were investigated in 5 mothers with deficient lactation and in their children soon after delivery. In addition, the transfer of metoclopramide into breast milk was evaluated in 18 mothers during the 8th to 12th puerperal weeks. Metoclopramide was detected in all the milk samples studied, generally at a higher concentration than in maternal plasma. Metoclopramide was found in plasma from only 1 of the 5 neonates studied. Exposure of the child to metoclopramide, estimated by multiplying the daily breast milk volume by the concentration of metoclopramide in the milk, ranged from 6 to 24 μg/kg/day for the 5 children in the early puerperium to 1 to 13 μg/kg/day for the 18 children during the late puerperium. These quantities are considerably less than the therapeutic dose of 500 μg/kg/day recommended for children. However, the plasma concentration of prolactin in 4 out of 7 neonates sampled taken during administration of metoclopramide to the mother were higher than the highest plasma prolactin level in children of same age of untreated mothers. The plasma concentration of thyrotrophin in the newborns remained within the normal range.

Key words: metoclopramide, breast milk level; transfer into milk, prolactin, thyrotrophin, maternal blood level, newborn blood level

Breast milk has been generally accepted as superior to milk substitutes in nutritional, anti-infectious, anti-allergic and psycho-emotional aspects (Jeliffe and Jeliffe 1977; Fleishman and Finberg 1979; Winikoff and Baer 1980). The International Federation of Gynaecology and Obstetrics has therefore recommended actions to encourage breast feeding and has stated that everything must be done to promote and facilitate it (FIGO News 1982). Because deficient lactation is often caused by inappropriate secretion of prolactin (Tucker 1979; Lunn et al. 1980), stimulation of pituitary prolactin release by an antidopaminergic agent, metoclopramide, has yielded a significant improvement in milk secretion by mothers with poor lactation (Souza 1975; Guzmán et al. 1979; Kauppila et al. 1981; Kauppila et al. 1982). No clinical side-effects appeared in mothers or children during this therapy. However, before recommending metoclopramide for wide use as a lactation-stimulating agent, its pharmacokinetics and possible endocrinological effects in children must be carefully evaluated. This need is further strengthened by the finding that metoclopramide is transferred into breast milk (Lewis et al. 1980).

In the present study the concentration of metoclopramide in maternal and neonatal plasma and breast milk was measured, and the exposure of the newborn to metoclopramide was estimated by direct and indirect measurements. In addition, the pituitary response of the newborn to metoclopramide was evaluated by measuring the plasma concentrations of thyrotropin and prolactin.

Material and Methods

Mothers

Mothers who had inadequate lactation during their stay in the delivery ward were told about the research project. After giving informed consent, 5 mothers participated in the trial during the early puerperium and 18 mothers during the late puerperium. All the

mothers were healthy and none was taking any other medication. The study protocol was approved by the Medical Ethics Committee of Oulu University.

Treatment

Treatment of 5 mothers was started between the 3rd to 9th days after delivery, and for 18 mothers between the 8th and 12th puerperal weeks. Each mother received metoclopramide 10 mg (Emperal®, Neofarma, Helsinki, Finland) 3 times daily for 2 weeks. Milk production during the early puerperium was estimated by subtracting the supplementary feed from the daily average need (165 ml/kg/day; see Anderson 1979), and in the late puerperium by weighing the child before and after nursing (Ylikorkala et al. 1980).

Plasma and Milk Samples

In early puerperium, control blood and milk samples were collected on the day preceding the start of the therapy. For kinetic studies maternal blood and milk samples were taken on the first day 0, 0.5, 1, 2, 3, 5 and 7 h after the first oral dose of metoclopramide. On the succeeding days blood and milk samples were taken at 9 a.m., 2 h after the morning dose of metoclopramide. Venous blood samples from the newborns were taken on the day preceding the therapy and on the 4th and 14th days of therapy, 2 h after the morning dose of metoclopramide.

In the late puerperium, breast milk samples were taken in the morning of the 9th to 11th days of therapy.

Blood samples were immediately centrifuged, and the plasma and milk samples were immediately frozen and stored at −20 °C until assayed.

Assays

Metoclopramide in plasma samples were determined by a slightly modified HPLC method from that of Graeffner et al. (1979). Metoclopramide in milk samples was purified by back extracting it into 1N HCl 1 ml from the first alkaline extraction. The acid phase was again made alkaline with 2N NaOH and was re-extracted with 2 ml dichloromethane. The organic phase was transferred to a clean centrifuge tube and evaporated to dryness under a stream of nitrogen. The residue was dissolved in 250 µl dichloromethane and 100 µl was injected into the column. The corresponding standard curves were obtained with blank breast milk samples spiked with same amounts of metoclopramide as in the plasma standards.

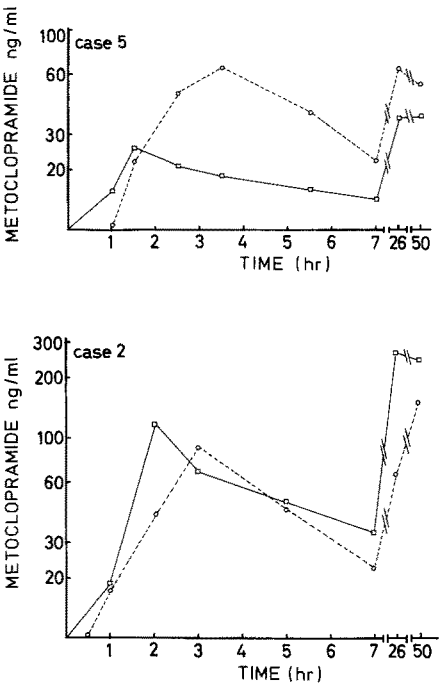

Fig. 1. Metoclopramide concentration in plasma and milk as a function of time after the first oral dose and on the second and third days, 2 h after the morning dose of metoclopramide. Plasma, solid lines; milk, interrupted lines

Plasma prolactin and thyrotrophin concentrations were measured by RIA following the instructions of the manufacturers: Diagnostic Products Corporation, Los Angeles, USA, for prolactin, and Corning, Medfield USA, for thyrotrophin.

Results

Metoclopramide Concentrations

The concentrations of metoclopramide in the milk were consistently higher than in the plasma in all but one mother (No. 2; Fig. 1). The peak maternal plasma levels occurred 2–3 hours after administration of the drug and were accompanied by or were rapidly followed by peak the concentration in milk. The approximate plasma half-life, calculated from the linear portion of the plasma concentration curve, varied between 2 and 5 h (mean 3.4 h). On the second and third days of therapy, plasma and milk concentrations were increased compared to those observed on the first treatment day. No significant accumulation occurred thereafter as was evident from the concentrations recorded on the 4th and 14th treatment days (Table 1). Individual concentrations varied greatly.

Table 1. Concentration of metoclopramide during the early puerperium in maternal plasma, breast milk and newborn plasma, and estimated maximum exposure of the newborn

Mother	Days in treatment	Metoclopramide concentration [ng/ml]			Weight of newborn [g]	Daily milk yield	Estimated maximum exposure [μg/kg/day]
		Maternal plasma	Milk	Newborn plasma			
1	4	76.0	156.5	<2	3680	550	23
2	4	194.4	105.6	20.9	3850	600	17
	14	293.0	153.5	18.8			24
3	4	67.7	92.5	<2	3500	500	13
	14	43.0	130.6	<2			19
4	4	17.7	71.9	<2	3100	350	8
5	4	36.8	51.7	<2	3000	350	6

Plasma samples were taken 2 h and milk samples 1 to 2 h after 10 mg metoclopramide p. o. Breast feeding occurred 0.5 to 1.5 h after the last dose; [a] maximum possible exposure was estimated by multiplying the volume of breast milk (165 ml/kg/day – supplementary feed) by the metoclopramide concentration in breast milk

Table 2. Concentration of metoclopramide in breast milk of mothers treated orally with metoclopramide during late puerperium. Exposure of the child to metoclopramide was estimated by multiplying the volume of milk by the concentration of metoclopramide in the milk sample

Subject	Milk yield/day [ml]		Metoclopramide concentration in breast milk [ng/ml]	Weight of child [g]	Estimated exposure to metoclopramide [μg/kg/day]
	Before therapy	On 9th day of therapy			
1	500	500	23.0	3500	3.3
2	200	240	60.0	6100	2.4
3	400	550	54.5	5250	5.7
4	320	720	26.5	4400	4.3
5	400	550	45.8	7000	3.6
6	520	800	82.0	5400	12.2
7	600	750	125.0	7100	13.2
8	800	1100	61.0	6400	10.5
9	420	530	21.0	4900	2.3
10	60	120	38.5	5500	0.8
11	380	550	33.0	5190	3.5
12	450	500	20.0	5300	1.9
13	180	150	43.5	5000	1.3
14	600	550	44.0	5500	4.4
15	800	1300	35.5	5500	8.4
16	500	1000	38.0	6000	6.3
17	400	500	86.0	6000	7.2
18	80	200	25.0	3300	1.5
Mean	423	589	47.9	5408	5.2
±SD	203	311	26.5	977	3.7

Metoclopramide was detected in the plasma sample from only one newborn, whose mother also had the highest concentrations in plasma and milk.

During the late puerperium, the concentration of metoclopramide in the milk varied from 20 to 125 ng/ml (Table 2), which is slightly less than the range of 28 to 157 ng/ml observed during the early puerperium. The estimated maximum exposure of the child to metoclopramide varied from 6 to 24 μg/kg/day during the early puerperium and from 1 to 13 μg/kg/day during late phase.

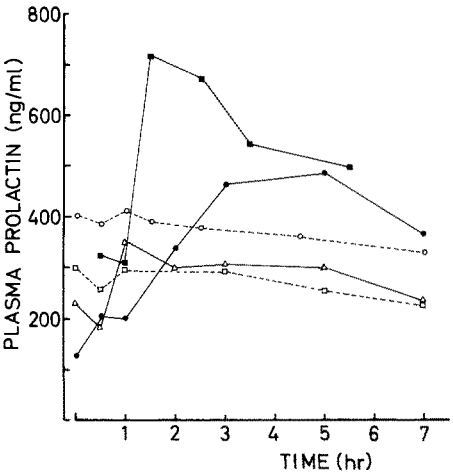

Fig. 2. Prolactin concentration in maternal plasma as a function of time after the first oral dose of metoclopramide

Prolactin and Thyrotrophin Concentrations

An oral dose of 10 mg metoclopramide rapidly increased the plasma prolactin concentration in 3 mothers. The prolactin level remained unchanged in the 2 mothers with the highest basal concentration of prolactin (300 ng/ml or more; Fig. 2). In all 5 women the prolactin level remained high throughout the investigation.

Plasma prolactin concentrations in the newborns were comparable to those in the mothers before medication. Although the concentration of prolactin tended to decrease during metoclopramide administration, in 4 out of 7 samples collected they were higher during treatment (275, 276 and 321 ng/ml on

the 4th day and 203 ng/ml on the 14th day of therapy) than the highest value (219 ng/ml on the 4th day and 176 ng/ml on the 14th day of therapy) in the control samples from neonates of same age born to untreated mothers.

Plasma thyrotrophin concentrations in the newborns did not change significantly during the study period and were never above the upper limit of the reference value for adults by our method of 12.3 mU/l.

Discussion

Many studies have demonstrated that centrally acting antidopaminergic agents, metoclopramide (Souza 1975; Guzmán et al. 1979; Kauppila et al. 1981; Kauppila et al. 1982) and sulpiride (Ylikorkala et al. 1982), which stimulate prolactin secretion, are potentially useful in improving breast milk excretion by mothers with poor lactation. The beneficial effect of metoclopramide was confirmed in this study. Because antidopaminergic agents affect the central nervous system, and they may have many side-effects (Jenner and Marsden 1979; Pinder et al. 1976), it is imperative to evaluate their fate and effects in the newborn before they come into wide-spread use.

In the present report metoclopramide has been shown to be transferred to breast milk in concentrations similar to or higher than those in maternal plasma. As a function of time the concentrations of metoclopramide in breast milk closely followed those in maternal plasma, albeit at a higher level. This indicates relatively rapid equilibration between maternal plasma and breast milk. The suggested tendency of basic drugs, like metoclopramide, to accumulate in the slightly acid milk (Rasmussen 1971) was not clearly evident in the present study. In addition, despite a high metoclopramide concentration in milk, the drug was detected in a concentration exceeding the limit of sensitivity of the method in plasma from only one newborn out of five. Even in this baby the estimated exposure was about 5% of the recommended daily dose for children, 500 μg/kg/per day.

The newborn, however, is not a miniature adult in terms of pharmacokinetics and pharmacodynamics. Consequently, the safety of the metoclopramide therapy must be evaluated within the context of existing knowledge of perinatal pharmacokinetics and pharmacodynamics. In adults, metoclopramide is mainly excreted unchanged or as a sulphate or glucuronide conjugate (Schulze-Delrieu 1981). Renal excretion and glucuronic acid conjugation of foreign chemicals are immature during the first few weeks after birth, but sulphate conjugation has been shown to compensate for the impaired glucuronide conjugation of the newborn, at least for certain drugs (for references, see Dutton and Leakey 1981). The situation with metoclopramide is not known at present. Although the elimination of metoclopramide in the newborn might be slower, due to immaturity of renal excretion and glucuronic acid conjugation, significant accumulation was not observed here.

Another potential problem is concerned with the pharmacodynamic actions of metoclopramide in the newborn. Is the newborn infant more, equally or less sensitive than the adult? In another study (Arvela et al. 1983), in which metoclopramide was administered before Caesarean section, metoclopramide concentrations in the newborn after placental transfer were mostly found to be 20 to 30 times higher than the concentrations in the present study after exposure via breast milk. Cavallo et al. (1980) showed that thyrotrophin levels in plasma from neonates typically remained within the adult range in the early days of life. Roti et al. (1983) recently reported that metoclopramide administered to pregnant women at term failed to affect the thyrotrophin level in the fetus. The preliminary data from the present relatively small series of subjects is consistent with that finding in that metoclopramide administered to mothers did not significantly change plasma thyrotrophin in the newborn, even though the plasma prolactin showed a tendency to increase. Thus, during the puerperal period of life, the pituitary lactotrophs but not thyrotrophs seem to be relatively sensitive to the centrally acting antidopaminergic agents. Although exposure of the newborn to metoclopramide via breast-feeding is intermittent and of relatively short duration, further studies are required to demonstrate whether the known adverse effects of dopaminergic receptor blocking agents (Rupniak et al., 1983) may affect the newborn in this way.

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