Acta Paediatrica Hungarica 31 (4), pp 415-422 (1991)

THE INFLUENCE OF METOCLOPRAMIDE ON THE COMPOSITION OF HUMAN BREAST MILK

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Received 4 February 1991

The breast milk prolactin (PRL) has been claimed to play a role in the control of electrolyte composition of the milk. Since metoclopramide has been shown to increase milk production in humans, we have made an attempt to investigate the production, the PRL and sodium concentrations in milk with (group I) and without (group II) maternal metoclopramide treatment (5 days, 30 mg/day). Both groups consisted of 11 mothers and their full-term newborn infants. The daily milk production was significantly higher in the treated group (276.4 ± 36.6 vs 150.9 ± 25.3 ml/day, $p<0.01$). The PRL measured by RIA was similar in the milk samples of the metoclopramide treated and control groups (80.5 ± 17.7 vs 90.7 ± 27.3 ng/ml). The sodium concentration in the milk of mothers taking metoclopramide was 22.1 ± 1.6 mmol/l and 24.3 ± 3.2 mmol/l in the control group ($p=0.59$). On the 5th postnatal day the plasma PRL of the newborns of mothers treated with metoclopramide does not differ from the values of the control babies (29.8 ± 2.6 vs 30.7 ± 2.4 ng/ml) indicating that the amount of metoclopramide transferred into the milk has no apparent influence on the hypothalamo-hypophyseal axis of the neonate. In conclusion: the maternal metoclopramide treatment augments the milk production without having any effect on the PRL and sodium concentration of human "mature" milk.

INTRODUCTION

Breast milk is undoubtedly the best food for infants /7, 20/ and mothers are advised to feed their babies with their own milk at least for 3 months. Prolactin (PRL) plays a critical role in the initiation and maintenance of lactation in humans /18, 19/. In some cases deficient lactation is caused by

inappropriate secretion of PRL and metoclopramide stimulates PRL secretion by occupying hypothalamic dopaminergic receptors and blocking dopamine's action as an inhibitor of PRL secretion /4, 5, 9, 11, 14, 15, 16/. Maternal metoclopramide treatment has been shown to augment milk production by elevating basal PRL level /12/, but it may also interfere with the hypothalamic response to suckling, and milk expression induced PRL release may not occur /5/.

PRL in milk is biologically potent /8, 10/ and has been claimed to play a role in the control of electrolyte composition of the milk. Irrespective of the length of gestation, the daily PRL excretion into the milk showed significant negative correlation with milk Na level and Na/K ratio /6/. Metoclopramide is transferred into breast milk and in a few cases elevated neonatal PRL levels were reported after maternal metoclopramide treatment /13/.

In the present study we decided to investigate the daily milk production, the daily milk PRL excretion, and the Na content of milk after maternal metoclopramide treatment. In addition, the pituitary response of the newborn to metoclopramide was evaluated by measuring the plasma concentration of PRL.

MATERIALS AND METHODS

Two groups of healthy lactating mothers volunteered for the study. None of them had a history of toxemia of pregnancy, renal disease or diuretic therapy. All of them had an uncomplicated vaginal delivery at term. They were on normal diet and the estimated daily sodium intake was about 100-120 mmol/day. Group I consisted of 11 mothers and their newborn infants. The mothers were taking 10 mg metoclopramide (Cerucal, GERMED, Berlin) in every 8 hours for 5 days, started at the first day after delivery. Group II included 11 mothers and their newborns without metoclopramide or any other medical treatment which could influence lactation. Clinical data of the enrolled mothers and their newborns are shown in Table I. There were no statistical differences between the two groups in parity, maternal age, gestational age, birth-weight, and Apgar score.

TABLE I

Clinical data of the enrolled mothers and their newborns

	Group I (treated)	Group II (control)
Maternal age (years)	25.2 (17-35)	24.9 (18-34)
Parity	1.6	1.5
Gestational age (weeks)	39.3 (37-41)	39.1 (37-40)
Birth weight (g)	3221 (2850-4230)	3462 (3000-4400)
Apgar score (1 minute)	8.8 (7-9)	8.9 (7-9)
n	11	11

Milk samples were obtained on the 5th day post partum at the beginning, and at the end of feedings by expressing, at least three times a day. The total amount of milk was estimated by weighing the baby before and after each feeding and/or by measuring the volume of the expressed milk. On the 5th postnatal day blood was taken from the newborn, after separating the plasma the samples were frozen and stored at -20 ^{o}C until analyzed by radioimmunoassay for PRL /2/. Sodium concentrations were determined by flame photometry. Milk PRL was measured as reported by Healy et al /10/ using SERONO-BIODATA kits. Statistical analysis was done by Student's t-test.

RESULTS

Maternal metoclopramide treatment in a dose of 30 mg/day, started after delivery, augmented significantly the daily milk production within 5 days. In group I the estimated milk expression was 276.4 $\pm$ 36.6 ml/day, meanwhile the milk production in group II was 150.9 $\pm$ 25.3 ml/day ($p<0.01$). The PRL and sodium concentrations in the milk samples of the mothers taking metoclopramide were 80.5 $\pm$ 17.7 ng/ml and 22.1 $\pm$

1.6 mmol/l, respectively, but no statistical differences were found compared to group II (90.7 ± 27.3 ng/ml and 24.3 ± 3.2 mmol/l). The neonatal plasma PRL levels were similar in both groups (29.8 ± 2.6 ng/ml in group I vs 30.7 ± 2.4 ng/ml in group II) on the 5th postnatal day. Results are listed in Table II.

TABLE II

Milk production, PRL, sodium concentrations and neonatal plasma PRL levels on the 5th postnatal day with (group I) and without (group II) metoclopramide treatment (mean ± SE).

	Group I (treated)	Group II (control)
Milk production ml/day	276.4 + 36.6	150.9 + 25.3 *
Milk PRL concentration ng/ml	80.5 + 17.7	90.7 + 27.3
Milk Na concentration mmol/l	22.1 + 1.6	24.3 + 3.2
Plasma PRL of the newborn ng/ml	29.8 + 2.6	30.7 + 2.4
n	11	11

* $p < 0.01$

DISCUSSION

Lactation results from complex interaction of hormones, although PRL appears to be the most important hormone involved in the initiation and maintenance of lactation /18, 19/. Maternal PRL levels continue to increase during gestation, consequently, the plasma PRL level is lower at preterm than at term delivery /3/. Metoclopramide - as an antagonist of dopamine - has been shown to induce lactation successfully /4, 5, 9, 11, 12, 14, 15, 16/. Guzmán et al /9/ and Kuappila et al /12/ pointed out that metoclopramide increased the basal PRL level and in a dose of 30 mg/day significantly elevated the

maternal serum PRL level and the daily milk production. Ehrenkrantz and Ackerman /5/ investigated the effect of metoclopramide therapy in women who delivered premature infants and the therapy was started at a mean of 32 days post partum. In agreement with previous results, the basal PRL level and the daily milk production increased within a few days after having started the therapy and lasted during the treatment. Besides, the same authors observed that milk expression did not produce any additional PRL response in the treated women /5/.

PRL is present in the human milk and may play some role in lactation, in the regulation of milk sodium content, and the intestinal absorptive function of the suckling neonate /6, 8, 10/. Yuen demonstrated that the foremilk contained significantly higher PRL concentrations than the hindmilk /21/. Foremilk serves mainly to provide hydration to the newborn rather than energy. Furthermore, women with galactorrhea and hyperprolactinaemia have been demonstrated to have twofold higher PRL concentration in the milk as compared to the plasma. After bromocriptine treatment both the plasma and the milk PRL concentration decreased, the concentration gradient remained, however, in favour of the breast milk /22/. Milk of lactating mothers receiving bromocriptine treatment had lower milk sodium levels compared to placebo taking controls /1/.

The pharmacokinetics and endocrinological effects of metoclopramide were investigated by Kuappila et al /13/. Metoclopramide was detected in milk samples, generally in higher concentration than in maternal plasma, but the estimated intake by the newborn was considered only 1 to 5% of the recommended therapeutic dose for children. Sulyok et al /17/ giving metoclopramide for premature babies noted an increase in urinary sodium excretion, a decrease of potassium excretion, and a decrease of plasma and urinary aldosterone concentration. The effect of metoclopramide therapy on the composition of human milk is not known. However, Kuappila et al /13/ found that 4 out of 7 breast-fed neonates sampled during maternal metoclopramide treatment had higher PRL concentration compared to the infants of untreated mothers. The plasma concentration

of thyrotropin in the newborns remained within the normal range.

In the present study mothers giving birth at term were given metoclopramide to improve milk production in a dose of 30 mg/day for 5 days, started after delivery. On the 5th postnatal day the daily milk production was significantly higher in the treated group compared to untreated mothers. No serious side effects were noted. The milk PRL and sodium concentrations were similar in both groups and the maternal metoclopramide treatment had no apparent influence on the neonatal PRL secretion indicating that the amount of metoclopramide transferred into the milk has no effect on the hypothalamo-hypophyseal axis of the neonate. The results could be partly explained by the lack of suckling-induced PRL release of metoclopramide treated mothers. Furthermore, we have to take into consideration the differences observed in the PRL concentrations of the foremilk and hindmilk. Further studies are needed to elucidate the long term effect of metoclopramide on the composition of human milk, especially after preterm delivery.

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