Br. J. clin. Pharmac. (1981), **12**, 855–858

ETHOSUXIMIDE IN HUMAN MILK AND IN PLASMA OF A MOTHER AND HER NURSED INFANT

ANDERS RANE & RAGNAR TUNELL

Departments of Clinical Pharmacology and Pediatrics at the Karolinska Institute, Huddinge Hospital, S-141 86 Huddinge, Sweden

1 The concentrations of ethosuximide were measured in the milk and in the plasma of a nursing mother and her infant during a period of 4.5 months after delivery.

2 The maternal and the infant's plasma concentrations rose after delivery.

3 The milk concentration of ethosuximide was similar to that in maternal plasma on the third day after delivery. During the following 2 months the average milk/maternal plasma concentration ratio was 0.80. The rise in ethosuximide concentration in milk during the first month was steeper than that in infant's plasma, which may be due to an increase in the infant's clearance of the drug.

4 Even if the infant had subtherapeutic plasma concentrations it is recommended to control the levels in infants that are nursed by ethosuximide-treated mothers when nursing has been established.

Introduction

Antiepileptic drugs are often used for periods of several years or decades. In most cases their use is inevitable during pregnancy and nursing and therefore, questions often arise as to the risk for the foetus or the nursed infant. Only scanty reports of the milk excretion of antiepileptics have been published (Erkkola & Kanto, 1972; Kaneko, Sato & Suzuki, 1979; Koup, Rose & Cohen, 1978; Pynnönen & Sillanpää, 1975; Rane *et al.*, 1974). Even though the quantitative measurements of the drug actually excreted into the milk and ingested by the nursed infant are important, the plasma concentrations achieved in the infant must also be taken into consideration. They reflect both the dose administered and the overall elimination capacity of the infant.

The maternal and the infant's plasma concentrations of ethosuximide as well as the milk concentrations are reported here for an epileptic mother and her child whom we studied for a period of almost 5 months after delivery.

Methods

The mother was 22 years old at the time of the study. She had suffered from petit mal epilepsy since the age of 8 years and had been treated only with ethosuximide since the age of 10 years. She had been maintained on a dose of 250 mg twice daily for the last 5 years before the study and during the pregnancy. The epilepsy was well controlled and no fits appeared during the pregnancy. Apart from the epilepsy she was healthy.

The pregnancy was uneventful and a healthy girl with a birth weight of 3070 g was born on January 7. Milk secretion started on the second day after delivery and breast-feeding was uncomplicated. The first blood samples were collected from the mother and the newborn on January 10. On January 12 the weight of the baby was 3040 g and the mother and infant were discharged from the hospital. The infant developed normally during the time of the study and never presented any symptoms which might have been related to the exposure to ethosuximide. The infant was breast-fed the whole time and no supplementary milk was given. At regular times the health status was checked at the outpatient paediatric clinic and blood samples were then obtained.

The purpose of the study was explained to the mother and her consent was obtained. Blood samples were collected by venepuncture of the mother and from the heel of the infant into heparinized tubes and capillaries, respectively. The blood samples were taken between 10.45 h and 12.30 h, i.e. about 3 to 5 h after the morning dose. On two occasions frequent blood samples from the mother and/or the infant were taken during the first 7 to 8 h of the dose interval, the first sample from the mother being taken before the morning dose.

Milk was collected simultaneously with the blood sampling. The breasts were emptied by pumping and the volume measured. After separation of aliquots (5–10 ml) for drug analysis, the infant was fed with the rest. Breast feeding was always performed at the habitual nursing times, either via the bottle or when drug analysis was not planned, directly.

0306–5251/81/120855–04 $01.00

Plasma was separated and stored at −20°C until analysis. Breast milk aliquots were frozen as such. Ethosuximide was analysed by a gas chromatographic technique (van der Kleijn *et al.*, 1973) in the maternal plasma and in the milk and by enzyme immunoassay (EMIT®, Syva Corporation) in the infant's plasma.

Results

The maternal plasma concentration increased after delivery and reached a peak after 1 to 2 months (Figure 1). Thereafter it decreased from the maximum concentration of 467 μM to 313 μM 4.5 months after delivery. There was a parallel change in the milk concentration of ethosuximide when milk samples were compared with the mother's plasma samples collected at the same time. The mean milk/maternal plasma concentration ratio on three occasions (January 18, February 11 and March 4) was 0.80 ± 0.06 (s.d.) whereas the corresponding ratio was 1.03 on the third day after delivery, i.e. when colostrum was secreted.

The infant's plasma concentrations rose from 155 μM on January 10 to a maximum of 209 μM 1 month later. Thereafter there was a gradual decrease in the plasma concentrations of ethosuximide despite continued and unaltered medication of the mother and without supplementary bottle feeding.

The plasma concentrations were somewhat variable in the mother during one dose interval (Figure 2). They increased from a predose level of 331 μM to a maximum of 385 μM. The infant's plasma

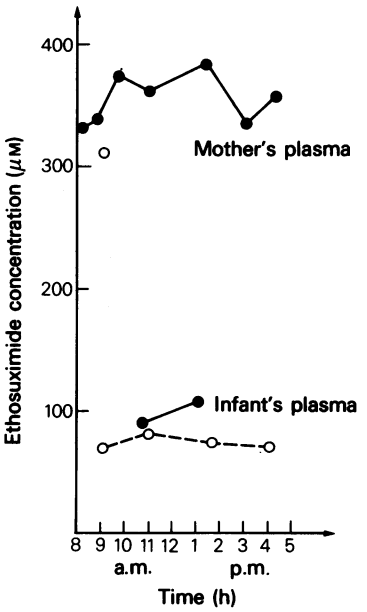

Figure 2 Plasma concentrations of ethosuximide in the mother and the infant on two different occasions (● May 6; ○ May 28) during a dosage interval. The first maternal concentration was measured prior to the morning dose.

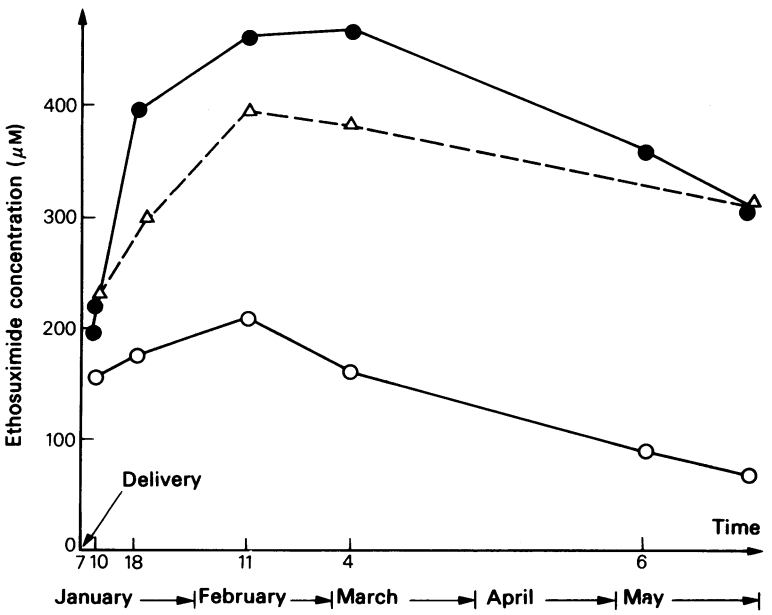

Figure 1 Plasma concentrations in the mother (●) and infant (○) and milk concentration (△) of ethosuximide during 4.5 months after delivery.

ethosuximide concentration was only about 30% of the average of the maternal concentrations. On another occasion one pre-dose concentration in the mother was compared with several concentrations in the infant. The latter varied only little during the dose interval and their average value was 24% of the mother's plasma concentration.

Discussion

Relatively high milk concentrations of ethosuximide were observed in our patient. The milk/plasma ratio of 0.80 is in accordance with the findings of Kaneko *et al.* (1979) who reported a ratio of 0.79. Their value was derived from several women, but the milk and blood sampling was not standardized in relation to dose, yet the samples were collected simultaneously in each subject. In another study (Koup *et al.*, 1978) paired samples of milk and plasma in an epileptic woman revealed a ratio of 0.94 ± 0.06.

Taken together, the current information on ethosuximide passage into human breast milk is consistent with low or negligible plasma protein binding of this drug (Barlow, Firemark & Roth, 1962) and with the assumption that the unbound fraction diffuses into the milk although there is no proof of this theory as yet. The high colostrum/plasma concentration ratio may be explained by specific binding to protein fractions secreted at high concentrations early in lactation. Several such proteins, such as lactoferrin, serum albumin, α-lactalbumin, immunoglobulins G and M, etc, are secreted at comparatively high concentrations during the first week(s) after delivery (Lönnerdal, Forsum & Hambraeus, 1976).

Of greater clinical interest than the milk concentrations is the actual plasma ethosuximide concentration that is achieved in the nursed infant over longer periods of time. These levels reflect the balance between the intake and output of drug in the newborn infant. Very little is known about the neonatal capacity to eliminate this drug. In older children direct (Buchanan, Fernandez & Kinkel, 1969; Chang, Dill & Glazko, 1972) or indirect (van der Kleijn *et al.*, 1973) evidence for a more rapid elimination of ethosuximide than in adults has been presented. Such data are commensurate with the clinical routine to give higher body weight related doses to epileptic children than to adult patients in order to achieve a certain plasma concentration (Sherwin & Robb, 1972). Koup *et al.* (1978) were able to estimate the serum half-life of ethosuximide in a newborn baby, who had been exposed to the drug *in utero* throughout the gestation. Their value of 41 h is close to those reported for older children; 31 (Buchanan *et al.*, 1969) and 24–30 h (Sherwin & Robb, 1972) at 7 to 9 and 3 to 10 years of age, respectively. The plasma half-life in adults averages 60 to 66 h (Buchanan *et al.*, 1969; Chang *et al.*, 1972). It is conceivable that the short half-life reported in a newborn patient (Koup *et al.*, 1978) may result partially from intrauterine induction of the drug metabolizing capacity. Such an induction is plausible to have taken place also in our newborn patient. Although we could not measure the half-life some data tend to indicate a rapid elimination in the newborn. Assuming a complete absorption of the drug (Goodman & Gilman, 1975) an apparent volume of distribution (V_d) of 0.69 l/kg (Buchanan *et al.*, 1969) and a total daily milk intake of 600 ml after one month (600 ml would contain 236 μmol = 33.3 mg) it was calculated according to the formula by Wagner *et al.* (1965) that the average steady-state plasma concentration in the infant would be approximately 280 μM at a half-life of 41 h. The measured steady-state concentration was only 209 μM after 1 month (on February 11th) indicating an even shorter half-life.

From Figure 1 it is also evident that the ratio between the infant's plasma/milk concentration decreases over the first month. This indicates that the neonatal elimination capacity increases since the plasma concentration did not increase in parallel with the milk concentration and even less so with the amount of drug ingested by the infant. These results could also reflect an increase in V_d and/or the body weight.

We have no explanation for the increasing and then decreasing steady-state concentrations of ethosuximide in the mother after delivery. A similar observation has previously been reported (Koup *et al.*, 1978).

In view of the subtherapeutic plasma levels of ethosuximide and the healthy status of our newborn patient, our data or those of others do not indicate that nursing during therapy with ethosuximide would be dangerous for the infant. The biological and psychological value of breast feeding during the neonatal period must also be taken into consideration. Further studies are, however, required before nursing during ethosuximide treatment can be generally accepted. It is recommended that the infant's plasma concentration of ethosuximide is controlled when breast feeding has been established.

This work was supported by grants from the Swedish Medical Research Council (14x–04496).

References

BARLOW, C.F., FIREMARK, H. & ROTH, L.J. (1962). Drug-plasma binding measured by Sephadex. *J. Pharm. Pharmac.*, **14**, 550–555.

BUCHANAN, R.A., FERNANDEZ, L. & KINKEL, A.W. (1969). Absorption and elimination of ethosuximide in children. *J. clin. Pharmac.*, **9**, 393–398.

CHANG, T., DILL, W.A. & GLAZKO, A.J. (1972). Ethosuximide. Absorption, distribution and excretion. In *Antiepileptic Drugs*, eds. Woodbury, D.M., Penry, J.K. & Schmidt, D., pp. 417–423. New York: Raven Press.

ERKKOLA, R. & KANTO, J. (1972). Diazepam and breast-feeding. *Lancet*, **i**, 1235–1236.

GOODMAN, L.S. & GILMAN, A. (1975). *The pharmacological basis of therapeutics*. 5th edition. New York: Macmillan.

KANEKO, S., SATO, T. & SUZUKI, K. (1979). The levels of anticonvulsants in breast milk. *Br. J. clin. Pharmac.*, **7**, 624–626.

KOUP, J.R., ROSE, J.Q. & COHEN, M.E. (1978). Ethosuximide pharmacokinetics in a pregnant patient and her newborn. *Epilepsia*, **19**, 535–539.

LÖNNERDAL, B., FORSUM, E. & HAMBRAEUS, L. (1976). A longitudinal study of the protein, nitrogen and lactose contents of human milk from Swedish well-nourished mothers. *Am. J. clin. Nutr.*, **29**, 1127–1133.

PYNNÖNEN, S. & SILLANPÄÄ, M. (1975). Carbamazepine and mother's milk. *Lancet*, **ii**, 563.

RANE, A., GARLE, M., BORGA, O. & SJÖQVIST, F. (1974). Plasma disappearance of transplacentally transferred diphenylhydantoin in the newborn studied by mass fragmentography. *Clin. Pharmac. Ther.*, **15**, 39–45.

SHERWIN, A.L. & ROOB, P.J. (1972). Ethosuximide. Relation of plasma levels to clinical control. In *Antiepileptic Drugs*, eds. Woodbury, D.M., Penry, J.K. & Schmidt, D., pp. 443–448. New York: Raven Press.

van der KLEIJN, E., COLLSTE, P., NORLANDER, B., AGURELL, S. & SJÖQUVIST, F. (1973). Gas chromatographic determination of ethosuximide and phensuximide in plasma and urine of man. *J. Pharm. Pharmac.*, **25**, 324–327.

WAGNER, J., NORTHAM, J.I., ALWAY, C.D. & CARPENTER, O.S. (1965). Blood levels of drugs at the equilibrium state after multiple dosing. *Nature*, **207**, 1301–1302.

(Received January 30, 1981)