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Diazepam and active metabolite in breast milk and their transfer to the neonate

Diazepam has for many years been widely used in labour and the puerperium. It is known that it can be secreted into breast milk, and if it is administered during labour and afterwards appreciable amounts may be transferred to the neonate who can only slowly metabolize it. Diazepam and its active metabolite, desmethyldiazepam, can be detected 10 days after single administration of the drug to the mother (Eliot *et al.*, 1975). Drowsiness in neonates has been attributed to diazepam and its active metabolites in breast milk (Patrick, Tilstone, and Reavy, 1972). A maternal concentration to milk concentration ratio of 10:1 for each compound has been reported (Erkkola and Kanto, 1972).

The relation between substances in the mother's blood and its transfer to breast milk is complex and related, not only to simple diffusion but also to ionization of the drug and the protein and fat binding properties of the substances (Rasmussen, 1973). Diazepam is highly protein bound and only the unbound fraction can pass through biological membranes. Ionized fractions will diffuse, however, and nonionized fractions will pass into milk.

Materials and methods

Nine breast feeding mothers were given diazepam for post-partum tranquillization of persistent hypertension, and maternal milk and simultaneous blood samples were obtained. Capillary blood samples were taken from the infants coincident with routine neonatal investigations and all samples were analysed by electron-capture gas-liquid chromatography (Baird, Hailey, and Malcolm, 1973). The infants were also closely observed for the clinical features associated with diazepam toxicity.

Results

Administration of diazepam during the week before delivery, the day of delivery, and during lactation were considered separately. The maximum maternal blood level of diazepam and desmethyldiazepam and the level in the breast milk, together with the level found in infant blood, were estimated and compared.

No adverse clinical affects were observed other than 3 cases of mild jaundice. This incidence was not thought to be exceptional. Two typical cases are represented in Fig. 1 and 2. The persistence of

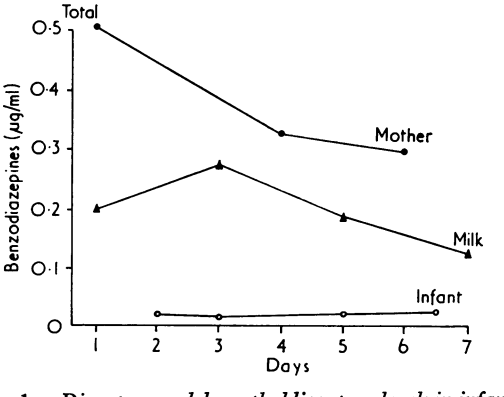

FIG. 1.—*Diazepam and desmethyldiazepam levels in infant blood after a single maternal dose of diazepam.*

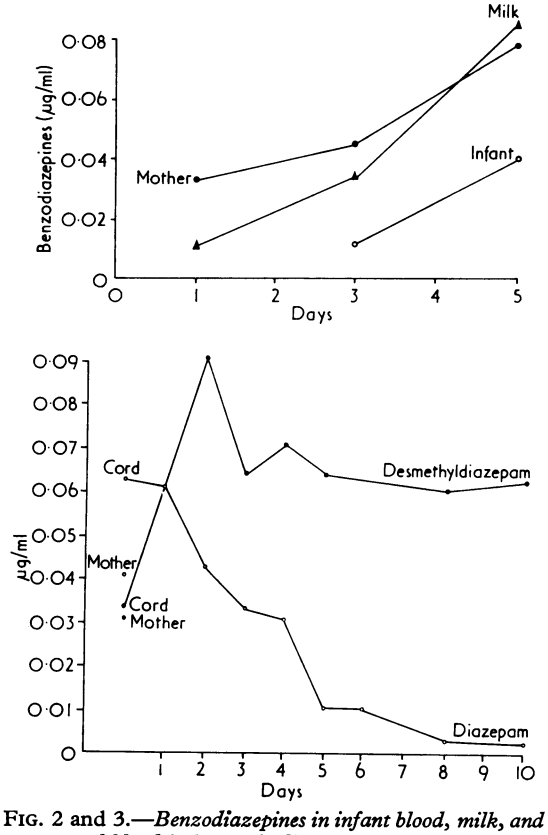

FIG. 2 and 3.—*Benzodiazepines in infant blood, milk, and maternal blood in breast feeding mothers on diazepam.*

diazepam and its active metabolite desmethyldiazepam after a single maternal dose during labour is further illustrated in Fig. 3.

Discussion

The ratios of maternal to milk levels of these substances were variable, ranging from 4·75:1 to 0·36:1, with an average of 2:1. This does not permit confident prediction and may be related in part to the lack of equilibration between maternal milk and blood in this short study, and also to the variable ease with which these infants took to the breast.

Appreciable amounts of active substances were detected in one infant 10 days after a single dose was given to the mother during labour. Diazepam is metabolized more slowly by the neonate than the adult (Morselli *et al.*, 1973), and therefore continued medication with diazepam to the lactating mother could lead to an accumulation of the drug and its active metabolite in the infant. This could theoretically lead to toxic levels in due course. If suitable alternative medication is not available, breast feeding should be discontinued.

Summary

Diazepam and its active metabolite, desmethyldiazepam, will pass from the mother's blood into breast milk. Measurable blood levels of the compounds then occur in breast-fed newborns. The infants metabolize these substances more slowly than adults and an accumulation of them in the infant is therefore possible.

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