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Excretion of tiapamil in breast milk

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The excretion of tiapamil in breast milk was studied in six lactating mothers (3–7 days post partum) following a single oral 600 mg dose of the drug. The milk/plasma ratio of tiapamil derived from the areas under the plasma and milk concentration–time curves was 0.44 ± 0.10 (mean ± s.d.). Assuming an intake of 350 ml of milk during a dosing interval of 12 h, the newborn would be exposed at the maximum to 0.053 mg tiapamil. This small amount does not represent a risk for the baby.

Keywords tiapamil calcium antagonist breast milk

Introduction

Tiapamil is an achiral phenylalkylamine type calcium antagonist, structurally related to verapamil (Ramuz, 1978). The compound is an antihypertensive (300–600 mg twice daily dosage regimen) and antianginal drug (e.g. Balansard *et al.*, 1984; Rhomberg *et al.*, 1983; Salorine *et al.*, 1983). Its preclinical pharmacology and toxicology (Eigenmann *et al.*, 1981a, b) and its pharmacokinetic characteristics in humans (Wendt, 1982; Hartmann *et al.*, 1983; Hinderling *et al.*, 1986) have been described. Tiapamil is a moderately lipophilic base with an octanol/water partition coefficient of 32 and a pK_A of 8.4. About 20% of the drug is eliminated by the kidney and its total plasma clearance amounts to 800 ml min^{-1}. The major metabolites present in plasma (desmethyltiapamil and the secondary amine) have much less pharmacological activity compared to that of the parent drug (Eigenmann *et al.*, unpublished results). About 75% of tiapamil in plasma is bound to proteins, predominantly to α_1-acid glycoprotein. The terminal elimination half-life ranges between 1.5 and 3 h. The drug has a large volume of distribution of 70–140 l indicating extensive tissue binding. The low oral bioavailability (15–40%) is ascribed to a pronounced presystemic elimination with a prehepatic component (Wendt, 1982).

Many drugs given to lactating mothers pass into breast milk and may represent a potential risk to the nursed infant. To evaluate this risk it is important to know the amount of drug reaching the infant. The excretion of drugs in breast milk and the factors affecting it have been reviewed in several reports (e.g. Wilson, 1981; Chaplin *et al.*, 1982; Findlay, 1983; Wilson *et al.*, 1985). No appropriate animal model for milk excretion exists and, therefore, studies of individual drugs in nursing women seem mandatory. Accordingly, the present study was undertaken to investigate the transfer of tiapamil into breast milk.

Methods

Subjects

Six lactating women, within 3–7 days post partum, participated in the study (Table 1). Before enrolment the subjects underwent a clinical examination to exclude hepatic, renal or cardiac dysfunction. At the end of the study the tests were repeated. No drugs were allowed during the study. The study was approved by the local Ethics Committee.

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Table 1 Demographic details of the subjects and their pharmacokinetic parameters

Subject	Age (years)	Weight (kg)	Day post partum	$t_{½,P}$ (h)	$t_{½,M}$ (h)	$R_{M/P}$	$Ae_M(12)$ (mg)
1	28	59	5	2.2	2.1	0.39	0.048
2	35	64	4	2.1	1.9	0.41	0.040
3	33	58	3	2.1	*	0.53	0.089
4	28	72	4	1.8	1.9	0.36	0.033
5	26	73	4	1.9	1.9	0.36	0.068
6	30	79	3	3.2	3.5	0.60	0.040
Mean	30	67.5		2.2	2.3	0.44	0.053
s.d.	3.4	8.5		0.50	0.70	0.10	0.021

* $t_{½,M}$ not estimated (see text).

Experimental protocol

After an overnight fast two 300 mg tablets of tiapamil were ingested together with 120 ml of tap water. Venous blood samples of 5 ml were drawn into citrated vacutainers immediately before and at 1, 2, 3, 4, 6, 8 and 10 h after drug intake. At the same time points samples of 5–10 ml of milk from either breast were collected by manual expression into sterile glass tubes. The pH of the milk samples was measured immediately after collection and, thereafter, the samples were stored at −20° C until analysis.

Sitting blood pressure and heart rate were measured at 0.5, 1 h and then at hourly intervals up to 10 h post dosing. During the study period the women received usual hospital food and the infants were given breast milk from other mothers.

Analytical methods

The concentrations of tiapamil in plasma were measured by normal phase h.p.l.c. (Heizmann *et al.*, 1984). The limit of assay was 20 ng ml^{-1} and the interassay coefficient of variation was 7%. For the measurement of tiapamil in milk, 0.5 ml of the milk sample was incubated with 100 µl of a suspension, containing 0.05 µg pronase (proteinase from *Streptomyces griseus*, supplied by SERVA Feinbiochemica, Heidelberg/FRG) in 1 µl of phosphate buffer pH 7, at 37° C over 1 h. After adjusting to pH 10 with borate buffer, further processing was performed as described for plasma. The limit of assay was 30 ng ml^{-1} and the interassay coefficient of variation was 10%.

Data analysis

The elimination half-lives of tiapamil in plasma and milk ($t_{½,P}$ and $t_{½,M}$) were calculated by linear regression of the terminal log-linear phases.

Total areas under the plasma or milk concentration *vs* time curves (AUC_P and AUC_M) were estimated by the logarithmic trapezoidal rule with extrapolation to time infinity using the concentrations at the last sampling times and the corresponding terminal half-lives (e.g. Gibaldi & Perrier, 1984).

The area under the tiapamil concentration–time curve in milk during a dosing interval of 12 h ($AUC_M(12)$) was calculated by

$$AUC_M(12) = AUC_M + \frac{C_M(\text{last})}{\lambda_{z,M}}(1-e^{-\lambda_{z,M}(t_{12}-t_{\text{last}})}) \quad (1)$$

where C_M(last) = milk drug concentration at last sampling time

t_{last} = last sampling time

$\lambda_{z,M} = 0.693/t_{½,M}$

In subject 3 the half-life $t_{½,M}$ could not be estimated due to unmeasurable drug concentrations in milk. Therefore, in this case AUC_M and $AUC_M(12)$ were calculated using $t_{½,P}$.

A time averaged milk/plasma ratio ($R_{M/P}$) of tiapamil was calculated from:

$$R_{M/P} = \frac{AUC_M}{AUC_P} \quad (2)$$

The total amount ($Ae_M(12)$) of tiapamil excreted in milk during 12 h was estimated by

$$Ae_M(12) = \frac{AUC_M(12)\ V_M(12)}{12} \quad (3)$$

$V_M(12)$ denotes the milk yield over 12 h, which was assumed to be 350 ml (Wilson, 1981; Whitehead & Paul, 1981). $Ae_M(12)$ is the maximum amount of drug that could be ingested by the

infant during the 12 h following single dose administration. Assuming linear kinetics the excreted amount ($Ae_{M,ss}(12)$) during a dosing interval of 12 h under steady state conditions may be extrapolated if AUC_M instead of $AUC_M(12)$ is inserted into equation 3.

Results

One hour after dosing of tiapamil subject 2 had transient tachycardia (110 beats min^{-1}), but without any subjective adverse effects. Otherwise no clinically noteworthy adverse events were encountered during the study period.

The average (geometric mean ± s.e. mean) tiapamil concentrations in plasma and breast milk of the six mothers are shown in Figure 1. Peak plasma concentrations were reached within 1 h after drug intake. The concentrations in breast milk were less than half of those in plasma and were generally parallel to those in plasma. In some milk samples beyond 6 h after dosing concentrations were below the limit of assay.

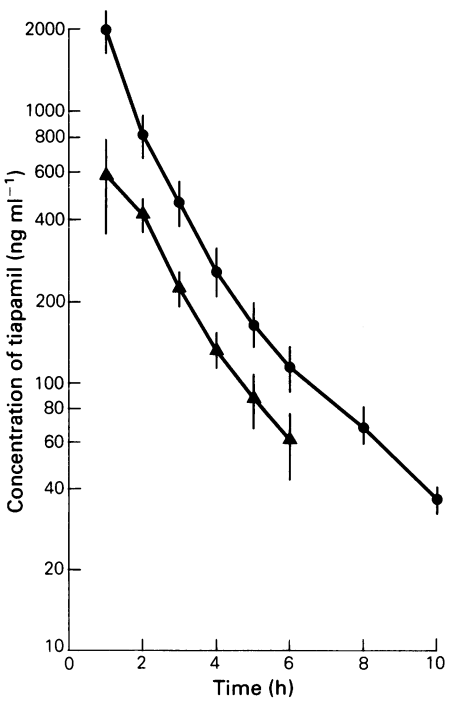

Figure 1 The average (geometric mean ± s.e. mean) concentration–time profiles of tiapamil in plasma (●——●) and breast milk (▲——▲) following a single oral 600 mg dose of tiapamil. At 8 h and 10 h after dosing only 3 and 1 data points, respectively, were available in milk and averages were not calculated.

The pharmacokinetic parameters of tiapamil are summarized in Table 1. Terminal half-lives were 2.2 ± 0.50 h and 2.3 ± 0.70 h in plasma and milk, respectively. The time averaged milk/plasma ratio (equation 2) was 0.44 ± 0.10. After the single 600 mg oral dose 0.053 ± 0.021 mg of tiapamil was excreted in breast milk (Table 1), when estimated on the basis of equation 3. From this it was estimated that 0.054 ± 0.022 mg would be excreted during a dosing interval of 12 h at steady state. The pH of all of the milk samples was 7.0.

Discussion

A biexponential decay of tiapamil plasma concentration and a terminal elimination half-life of about 2 h was consistent with previous findings (Wendt, 1982; Hartmann *et al.*, 1983).

The rapid equilibration of the drug between plasma and milk (within 1–2 h after dosing) and the parallel decay with time in both fluids indicate that tiapamil is rapidly redistributed from milk into plasma. Otherwise, the half-life of elimination in milk would be much longer than that in plasma, as can be estimated from a clearance of 350 ml 12 h^{-1} and a compartmental distribution volume of about 500 ml.

The milk/plasma ratio of tiapamil was found to average 0.44 whereas that for its congener verapamil was 0.6 when derived from a few patients after multiple dose administration (Miller *et al.*, 1986; Anderson *et al.*, 1987). In a further patient treated with verapamil a ratio of 0.23 was found (Andersen, 1983).

The amount taken up during a dosing interval is indicative of the exposure of the infant to the drug. Assuming a milk intake of 350 ml 12 h^{-1} the maximum amount of tiapamil that could have been ingested by the present group of newborns was estimated to be 0.053 mg. On a weight basis the maternal dose was 10 mg kg^{-1}, hence the babies (assumed weight: 3 kg) would have been exposed to 0.018 mg kg^{-1}, which represents less than 0.2% of the maternal dose. Exposure of the infant may be reduced further if mothers were to refrain from feeding during the first 3–4 h after drug administration.

In comparison the ingested (body weight related) doses of verapamil were estimated to range between 0.1 and 0.2% of the maternal dose (Andersen, 1983; Anderson *et al.*, 1987, Miller *et al.*, 1986).

The estimates for tiapamil are based on results following single dose application. However, the rapid equilibration of drug between plasma and milk should allow extrapolation from disposition

after a single dose to that during a multiple dose regimen. On the other hand transfer of drugs into breast milk may depend on several maternal physiological variables such as hormonal status and local haemodynamics and these will be changing in the course of a day and during different lactation periods (Wilson, 1983). Variation in the milk yield and changes in its pH and content of fat and protein are also important determinants of the amount of drug excreted (Syversen & Ratke, 1985; Fleishaker *et al.*, 1987). A methodological variable may arise from the collection of milk by manual expression which may influence the fat content of the sample (Spencer & Hull, 1981). However, we believe that these considerations are unlikely to alter our estimates of the excreted amount of tiapamil significantly.

Although nothing is known about the disposition of tiapamil in infants or their response to the drug, the very low doses ingested with milk (maximum 0.2% of the maternal dose on a body weight basis), are unlikely to be of any clinical consequence.

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