

## Pseudoephedrine and triprolidine in plasma and breast milk of nursing mothers

J. W. A. FINDLAY, R. F. BUTZ, J. M. SAILSTAD, J. T. WARREN & R. M. WELCH

Department of Medicinal Biochemistry, The Wellcome Research Laboratories, Research Triangle Park, North Carolina, USA

- 1 Plasma and milk concentrations of pseudoephedrine and triprolidine were determined (by radioimmunoassay) in three lactating mothers over 12–48 h after ingestion of a combination medication containing 60 mg of pseudoephedrine hydrochloride and 2.5 mg of triprolidine hydrochloride monohydrate.
- 2 Pseudoephedrine concentrations in milk were consistently higher than those in plasma. The total amount of drug in milk, as judged by areas under the respective curves (AUC), was two to three times greater than in plasma.
- 3 Triprolidine concentrations in milk and plasma were more variable between subjects than those of pseudoephedrine. AUC values for milk and plasma were similar for one subject, while the plasma value exceeded that for milk in another woman.
- 4 The fraction of the dose excreted in milk was estimated to be 0.4–0.7% for pseudoephedrine and 0.06–0.2% for triprolidine.

**Keywords** pseudoephedrine triprolidine breast milk

### Introduction

Quantitative studies of drug excretion in breast milk have been, until recently, rather uncommon in the medical and scientific literature, although the field has been reviewed on numerous occasions (Anderson, 1977; Findlay, 1983; Knowles, 1965; Welch & Findlay, 1981; Wilson *et al.*, 1980). In a recent review of progress in this area, Wilson and coworkers (1980) emphasized the lack of quantitative studies of drug distribution in human breast milk. A number of recent and more definitive studies (Findlay *et al.*, 1981a; Liedholm *et al.*, 1981, 1982; Lonnerholm & Lindström, 1982; Stéen & Rane, 1982) published on a variety of therapeutic drug types also reflect the rapidly growing awareness that detailed investigation of this field with the use of modern analytical techniques has been neglected until the past

several years. Since a variety of drugs may be prescribed for mothers during the period of infant nursing, and because a majority of mothers now breast feed their babies for some period after birth, questions about the safety of nursing the infant while taking medication often arise in pediatric practice. In this report we present results of a study on the distribution of a commonly used combination of the anti-histamine, triprolidine, and the decongestant, pseudoephedrine, between breast milk and plasma of three nursing mothers. To our knowledge, there are no definitive data on the entry of antihistamines or decongestants into human breast milk and this information should be of assistance to the practising pediatrician.

Some data from this study were presented in preliminary form at the Second Symposium on

Drug Disposition in Man, Sarasota, Florida, November 1981 (Findlay, 1983).

## Methods

### Clinical

**Subjects** All three subjects were healthy white females who were nursing healthy infants. Subject 1 was a 30 year old woman (weight, 50.8 kg) in the 14th week of infant nursing, subject 2 was a 32 year old (weight, 64.9 kg) who had been nursing for 18 months and subject 3 was a 27 year old (weight, 58.6 kg) who had been breast feeding her infant for 14 weeks. All subjects gave informed consent to participate in the study.

**Procedures** Each subject fasted for approximately 10 h prior to the start of the study and food was withheld for 1 h after drug ingestion, at which time a light breakfast was eaten. Thereafter, normal meal routines were resumed. These mothers had not taken any medications during several days preceding the study. A tablet of an antihistamine-decongestant combination product (Actifed®, Burroughs Wellcome Co., Research Triangle Park) containing 2.5 mg triprolidine hydrochloride and 60 mg pseudoephedrine hydrochloride was taken by mouth, followed by 200 ml of water. With the exceptions noted below, blood and breast milk samples were collected from these subjects as follows: blood samples (7 ml) were collected into evacuated glass tubes (Vacutainer®, Becton Dickinson and Co., Rutherford, New Jersey, USA) containing ethylenediaminetetraacetic acid disodium salt (EDTA) prior to drug administration and at approximately 0.5, 1, 2, 4, 6, 12 and 24 h after dosing. Subject 3 provided a 7.5 h rather than a 12 h sample and did not provide a 24 h sample. Subject 1 provided blood samples only at 1, 3 and 12 h after drug administration. Plasma was separated by centrifugation at 4°C and stored at -20°C until analysed for drug content. Milk samples were provided by subjects 2 and 3 at approximately 0.5, 1, 2, 4, 6, 12 (or 7.5 for no. 3) and 24 h after dosing, while subject 1 collected milk at approximately 0.5, 1, 1.5, 2, 3, 4, 7, 12, 14, 24, 36 and 48 h after drug ingestion. In each case, samples of breast milk were obtained prior to drug administration (blank breast milk). Breast milk samples (5–10 ml) were collected by manual expression and, for subjects 1 and 2, were mixtures of roughly equal volumes from each breast. In the case of subject 3, samples from each breast were analyzed

separately. Milk samples were stored frozen (-20°C) until analyzed. All sample time points shown in Figure 1 represent actual rather than scheduled collection times.

### Drug analytical procedures

Details of both pseudoephedrine (Findlay *et al.*, 1981b) and triprolidine (Findlay *et al.*, 1984) radioimmunoassay (RIA) procedures have been published elsewhere. Thus, only procedures for extraction of drugs from milk will be described. All assay points were run in duplicate.

**Tripolidine analysis in milk** Milk (0.2 ml) was treated with 0.5 M Na<sub>2</sub>PO<sub>4</sub> (pH 7.5, 0.2 ml) and extracted twice with benzene (4 ml) by mechanical shaking for 10 min in an extraction tube. After centrifugation the combined benzene layers were extracted similarly with 0.05 N HCl (1 ml). The aqueous layer was separated by centrifugation, treated with 0.5 M Na<sub>2</sub>PO<sub>4</sub> (pH 7.5, 0.4 ml) and extracted again with benzene (4 ml) as described above. The final benzene layer obtained after centrifugation was evaporated to dryness under a stream of dry nitrogen and the residue was dissolved in ethanol (50 µl) and then diluted in RIA assay buffer (0.95 ml). Aliquots (200 µl) of each reconstituted extract were taken for RIA as described previously (Findlay *et al.*, 1984). Blank breast milk samples to which triprolidine hydrochloride had been added were processed along with the unknown samples to provide internal standards and controls.

**Pseudoephedrine analysis in milk** Milk (1 ml) was placed in a 15 ml screw cap culture tube and basified by addition of 2 N sodium hydroxide (0.5 ml) in saturated sodium sulphate. This mixture was extracted twice with cyclopentane: diethyl ether (1:1, 7 ml) by mechanically shaking for 15 min. After centrifugation, the lower (aqueous) layer was frozen in a dry ice-acetone bath, and the organic solvent layer was decanted. The combined solvent extracts were treated with 0.05 N hydrochloric acid and shaken as above for 15 min. The solvent layers were separated by centrifugation and the aqueous acid layer was frozen as above. The organic layer was decanted and the aqueous acid layer containing the extracted pseudoephedrine was thawed and analysed by RIA as described previously (Findlay *et al.*, 1981b). The standard solutions for the RIA were prepared by extraction of a 1000 ng/ml solution of pseudoephedrine in blank human breast milk prepared by adding a solution of pseudoephedrine hydrochloride to milk. This internal

standardization corrected for losses in recovery, and was substantiated by separate extraction of three independently prepared milk control solutions at concentrations of 1000, 500 and 250 ng/ml pseudoephedrine (base equivalent).

#### Pharmacokinetic calculations

Areas under the concentration–time curves for plasma and breast milk were determined by the trapezoidal rule. Drug half-lives ( $t_{1/2}$ ) in plasma and breast milk were determined from the equation  $t_{1/2} = 0.693/\beta$ , where  $\beta$  is the terminal disposition phase rate constant which was calculated by least squares linear regression of the post-absorption portion of the respective concentration–time curves. Average drug concentration ( $C$ ) in milk over a given period of time ( $t$ ) was calculated from

$$C = \frac{AUC^t}{t}$$

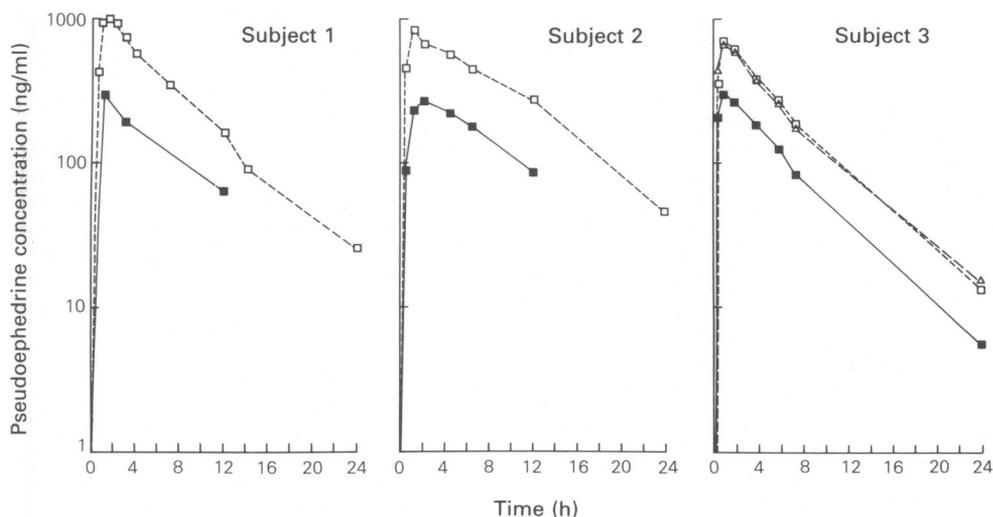
Calculations of amounts of drugs excreted in milk assumed a generous estimate of 1000 ml of milk secreted per 24 h period.

#### Results

Pseudoephedrine was detectable in all of the samples collected, with the exception of the 48 h milk sample collected from subject 1. The plasma and milk pseudoephedrine concentration–time profiles for all three subjects are presented in Figure 1. Milk concentrations were

consistently higher than plasma concentrations. The drug entered milk readily, reaching maximum concentrations at 1 or 1.5 h in all cases. Data shown for subjects 1 and 2 are for pooled milk samples from both breasts, but subject 3 provided separate milk samples from right and left breasts and these individual data for this mother are shown in Figure 1. No difference in pseudoephedrine milk concentration–time profile was seen between the two breasts.

Some pharmacokinetic parameters for these subjects are shown in Table 1. The type of data derived from each subject differs somewhat, since the frequency and extent of plasma and milk sampling varied slightly between subjects. Thus, insufficient plasma samples were obtained from subject 1 to allow definition of the area under the concentration–time curve (AUC) for plasma. In this case milk:plasma concentration ratios at 1, 3 and 12 h (2.6–3.9) after drug administration showed the same trend in favour of higher pseudoephedrine milk concentrations that the AUC ratios for subjects 2 and 3 exhibited (2.2–2.8). In subjects 2 and 3 enough plasma concentration data were obtained to allow calculation of the  $t_{1/2}$  in milk and plasma. The  $t_{1/2}$  in both fluids agreed well for both subjects, with a range of 4.2–7 h. The average pseudoephedrine concentration in plasma over 12 or 24 h periods was calculated from the AUC values, and, assuming a generous milk secretion of 500 ml/12 h, the amount of pseudoephedrine excreted was calculated to be 0.25–0.33 mg of base equivalent or 0.5–0.7% of the dose ingested by the mothers.



**Figure 1** Concentration-time profiles for pseudoephedrine in plasma (■) and milk (□) of nursing mothers. Subject 3 □ right milk, △ left milk.

**Table 1** Pharmacokinetic parameters for pseudoephedrine

Subject	Milk:Plasma concentration ratio at time (h)			$t_{1/2}$ (h)	Plasma $AUC_{0-12}^{12*}$	$AUC_0^{24*}$	$t_{1/2}$ (h)	Milk $AUC_0^{12*}$	$AUC_0^{24*}$
	1	3	12						
1	3.3	3.9	2.6				4.2		6451
2				5.9	2153		7.0 (5.6) †††	5972	7906
3				3.9		2143	4.1		4673

\* ng ml<sup>-1</sup> h\*\* Average concentration in milk over time  $t = AUC_t/t$ .

† Assuming 500 ml of milk secreted in 12 h, 1000 ml milk secreted in 24 h.

†† After a single dose.

**Table 2** Pharmacokinetic parameters for triprolidine

Subject	Milk:Plasma concentration ratio at time (h)			$t_{1/2}$ (h)	Plasma $AUC_{0-12}^{12*}$	$AUC_0^{24*}$	$t_{1/2}$ (h)	Milk $AUC_0^{12*}$	$AUC_0^{24*}$
	1	3	12						
1	0.5	1.2	0.7				2.8		37.2
2				4.8	115.2		11.9 (18.7) †††	64.9	106.6
3				5.8		58.3	9.5		29.0

\* ng ml<sup>-1</sup> h\*\* Average concentration in milk over time  $t = AUC_t/t$ .

† Assuming 500 ml of milk secreted in 12 h, 1000 ml milk secreted in 24 h.

†† After a single dose.

Data on triprolidine in the plasma and breast milk of the three subjects are shown in Figure 2 and pharmacokinetic parameters for this drug are given in Table 2. In contrast to the case of pseudoephedrine (*cf.* Figure 1) triprolidine concentrations in breast milk and plasma were similar, and, as for pseudoephedrine, no difference in drug concentrations in milk from left or right breast of subject 3 was noted. Some basic pharmacokinetic parameters for triprolidine in these mothers are given in Table 2. For subject 1 milk:plasma concentration ratios at 1, 3 and 12 h after drug administration ranged from 0.5–1.2, indicating no concentration of triprolidine in breast milk. This was confirmed by the more reliable comparison of milk:plasma AUC ratios in subjects 2 and 3, which gave values of 0.56 and 0.50, respectively. Calculation of the 24 h milk excretion of triprolidine, as described for pseudoephedrine, led to values of 0.001–0.004 mg of base equivalent, representing 0.06–0.2% of the dose ingested by the mother. In contrast to the pseudoephedrine case, the  $t_{1/2}$  of triprolidine appeared to be somewhat longer in breast milk than in plasma.

## Discussion

There is a clear-cut difference in the relative extent of entry of these two drugs into breast milk. Although both drugs are weak bases, there are differences in physicochemical properties between the two. Thus, pseudoephedrine has a pKa value of 9.22 (Benezra & McRae, 1979) while triprolidine has values of 3.6 and 9.3 (Benezra & Yang, 1979). Since the lower ionization constant for triprolidine would be expected to have little effect on the overall extent of drug ionization in the pH ranges of milk and plasma (6–7.4), the ionization characteristics at these pH values should be similar for both drugs. The octanol/water partition coefficients for triprolidine (Benezra & Yang, 1979) (7.0 at pH 7.4) and pseudoephedrine (Benezra & McRae, 1979) (0.049 at pH 6.0) suggest that the more lipophilic drug, triprolidine, might be expected to penetrate more readily into breast milk than pseudoephedrine. Since this is clearly not the case, some factor other than those mentioned above must be involved. One such parameter which has not

<i>Milk:Plasma</i> <i>AUC ratio</i>	<i>Average**</i> <i>concentration</i> <i>in milk (ng/ml)</i>		<i>Drug excreted</i> <i>in milk (mg)†</i>		<i>% Dose excreted</i> <i>in milk††</i>	
	<i>0-12 h</i>	<i>0-24 h</i>	<i>12 h</i>	<i>24 h</i>	<i>12 h</i>	<i>24 h</i>
		269		0.269		0.6
2.77Δ	498	329	0.249	0.329	0.5	0.7
2.18ΔΔ		195		0.195		0.4

††† Calculation including 24 h data point.

Δ  $AUC_{0-12}^{12}$  ratio.

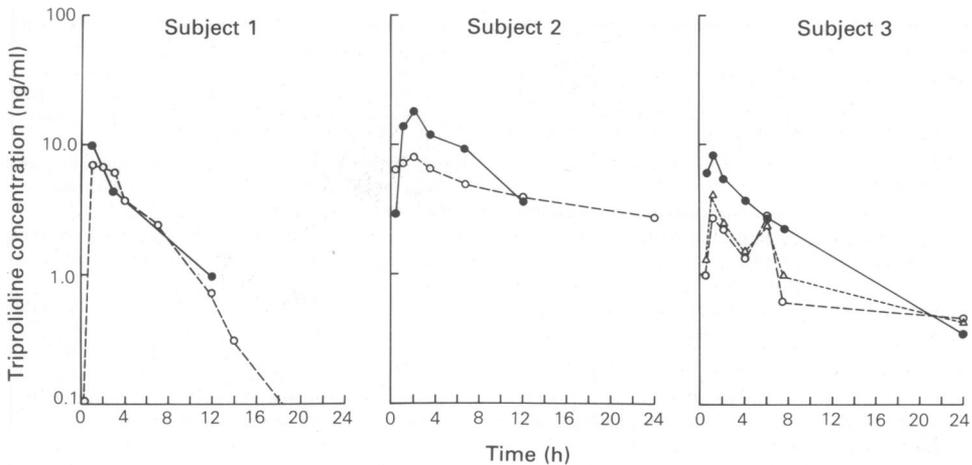
ΔΔ  $AUC_{0-24}^{24}$  ratio.

<i>Milk:Plasma</i> <i>AUC ratio</i>	<i>Average**</i> <i>concentration</i> <i>in milk (ng/ml)</i>		<i>Drug excreted</i> <i>in milk (mg)†</i>		<i>% Dose excreted</i> <i>in milk††</i>	
	<i>0-12 h</i>	<i>0-24 h</i>	<i>12 h</i>	<i>24 h</i>	<i>12 h</i>	<i>24 h</i>
		1.6		0.002		0.1
0.56Δ	5.4	4.4	0.003	0.004	0.1	0.2
0.50ΔΔ		1.2		0.001		0.06

††† Calculation including 24 h data point.

Δ  $AUC_{0-12}^{12}$  ratio.

ΔΔ  $AUC_{0-24}^{24}$  ratio.



**Figure 2** Concentration-time profiles for triprolidine in plasma (●) and milk (○) of nursing mothers. Subject 3 ○ right milk, Δ left milk.

been studied in detail for either of these drugs is the comparative extent or strength of their binding to proteins in plasma or milk. If binding of triprolidine to plasma proteins was much greater than that of pseudoephedrine, then the observed results on breast milk penetration may not be surprising. However, the variability in triprolidine milk levels, combined with the limited number of subjects participating in the study, make it difficult to draw firm conclusions on the extent of triprolidine excretion in milk. The pattern of relative milk:plasma drug concentration profile found for pseudoephedrine in the present study is similar to that found earlier for codeine (Findlay *et al.*, 1981a), another weak base which is not extensively bound to plasma proteins. The lower pH of breast milk relative to plasma results in a 'trapping' of weak bases in the ionized form.

The significance of our findings can be evaluated only in the clinical setting, and indeed may

already have been. We are aware of no published reports of adverse reactions in nursing infants to the triprolidine hydrochloride-pseudoephedrine hydrochloride combination, or its individual constituents. Our calculations (Tables 1 and 2) suggest that approximately 0.4–0.6% of the pseudoephedrine dose or 0.06–0.2% of the triprolidine dose ingested by the mother should be excreted in the breast milk over 24 h after a single dose. The actual amount excreted would be somewhat higher on a steady state regimen, but still quite low, and probably not high enough to warrant cessation of nursing. The mitigating factors in such a decision clearly would include the relatively lower weight (on a per kg basis) of the infant and the effect of the relative immaturity of the neonatal kidney in eliminating pseudoephedrine which is largely cleared unchanged in man by renal excretion (Brater *et al.*, 1980; Bye *et al.*, 1975; Lai *et al.*, 1979).

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