

## Mexiletine in human blood and breast milk

ANGELA M. LEWIS†  
M.B. B.S.

A. JOHNSTON\*  
B.Sc.

LATA PATEL\*  
B.Sc.

P. TURNER\*  
M.D., M.R.C.P.

Departments of †Obstetrics & Gynaecology, and \*Clinical Pharmacology, St Bartholomew's Hospital, London EC1A 7BE

### Summary

Twelve paired samples of breast milk and blood were obtained, between the 2nd and 5th days after she had given birth, from a 30-year-old woman who was on 8-hourly propranolol (20 mg) and mexiletine (200 mg). Propranolol was detectable in 9 of the samples of blood and in only 4 of the milk samples. Mexiletine was measurable in all samples, and the milk : plasma ratio varied between 0.78 and 1.89 with a mean of 1.45. However, the large volume of distribution of mexiletine makes it unlikely that the small dose of the drug received from the milk would be detrimental to the health of infants.

### Introduction

Information on drug transfer in breast milk from nursing mothers to infants is lacking for the majority of drugs (Wilson *et al.*, 1980) and it is therefore difficult for the physician to make a rational decision whether a mother undergoing drug treatment should continue to breast-feed her child. Recently, the authors have had the opportunity of studying milk/blood drug concentrations in a nursing mother taking both the  $\beta$ -adrenoceptor antagonist, propranolol, and the anti-dysrhythmic drug, mexiletine.

### The patient

The mother was a 30-year-old Lebanese who had had episodes of palpitations for 8 years. She was first seen by cardiologists when 10 weeks pregnant and a 24-hr ECG recording showed occasional ventricular ectopic beats and runs of ventricular tachycardia. Procainamide was administered for one month but produced no change in incidence of ectopic beats, and mexiletine 200 mg 8-hourly was therefore substituted. Propranolol 20 mg 8-hourly was added 3 days later. Five months later she was admitted in labour and a healthy infant was delivered by forceps under epidural anaesthesia and amoxicillin cover. Twelve paired samples of breast milk

and blood were obtained between the 2nd and 5th day after delivery.

### Methods and results

Propranolol was estimated in the samples by spectrofluorimetry and mexiletine by gas chromatography. Calibration samples were prepared in whole blood and cow's milk for both drugs.

The concentrations of propranolol found were low in both milk and blood and were consistent

TABLE 1. Breast milk and blood concentrations for propranolol (ND= None detectable)

Time after birth (hr)	Propranolol concentration (ng/ml)	
	Breast milk	Blood
44-15	ND	11
48-5	1	19
60-75	ND	16
66-5	5	41
69-5	ND	ND
81-5	ND	ND
84-75	2	38
88-5	ND	3
91	ND	ND
93-5	ND	30
105-5	ND	47
108-25	1	11

with the low dose given (Table 1.). Figure 1 shows the milk and blood mexiletine concentrations over time. The mean peak concentration of mexiletine was 724 ng/ml in blood and 959 ng/ml in milk.

The pH of the milk was measured using a pH meter and the mean milk pH was calculated by averaging the hydrogen concentration of these samples. The milk : plasma drug concentration ratio for mexiletine varied between 0.78 and 1.89 with a mean of  $1.45 \pm 0.3$  (s.d.) which is higher than would be predicted on the basis of pH partitioning:

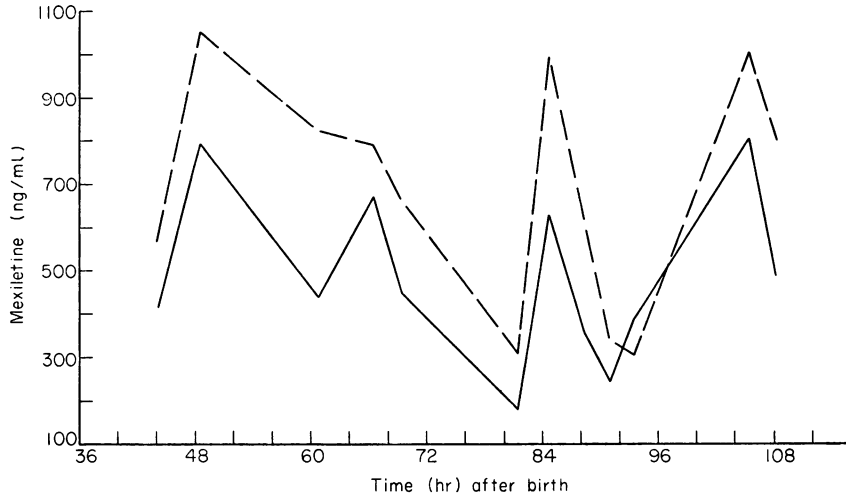


FIG. 1. Mexiletine concentrations found in milk (---) and blood (—) of the nursing mother are plotted against the time in hours after the birth of the child.

$$\text{Milk/blood concentration ratio} = \frac{1 + 10^{(pK_a - \text{pH milk})}}{1 + 10^{(pK_a - \text{pH blood})}}$$

substituting the measured value of mean milk pH 7.30 and blood pH 7.4 and mexiletine pKa of 9.05 the calculated ratio is 1.25. However, in this simplified form the equation assumes equal protein binding in blood and milk which has not been established.

### Discussion

The partitioning of propranolol into breast milk is small, confirming the observations of Bauher *et al.* (1979) who found milk : plasma ratios of between 0.4 and 0.7.

In the case of mexiletine, the milk : plasma ratio found in the present patient varied between 0.8 and 1.9, i.e. the concentration of mexiletine in milk generally exceeded that in plasma. In a recent study, Timmis, Jackson and Holt (1980) measured 2 paired milk and plasma samples and found ratios of 2.0 and 1.1. However, although mexiletine, like propranolol, is a lipid-soluble basic drug and can be expected to cross the placenta and gain access to the fetus, the suckling infant is unlikely to ingest a large amount of the drug.

Assuming an average daily intake of 0.5 litre of milk and a maternal plasma mexiletine concentration of 2.0 µg/ml it is unlikely that the infant would receive more than 1.25 mg of mexiletine in any 24-hr period. The daily adult dose of mexiletine required to produce therapeutic blood concentrations is 8–10 mg/kg and it has been shown that the dose must be increased to produce similar blood con-

centrations in infants (Holt, *et al.*, 1979). It is unlikely, therefore, that the amount of mexiletine ingested *via* breast milk would be detrimental to the child.

Anti-dysrhythmic drugs may be prescribed to women of child-bearing age and it is important, therefore, to know their plasma/breast milk ratios. This study demonstrates that observed ratios may vary from those predicted from kinetic equations based on known variables. Ratios are known for few anti-dysrhythmic drugs. A. Blackett and P. Turner (personal communication) have found a breast milk : plasma ratio of 0.6 for quinidine in one paired sample. Further studies are required to demonstrate the safety of breast feeding by women taking other anti-dysrhythmic drugs.

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