

## DISOPYRAMIDE AND ITS N-MONODESALKYL METABOLITE IN BREAST MILK

D.B. BARNETT

Department of Pharmacology and Therapeutics, Clinical Sciences Building, Leicester Royal Infirmary, Leicester

S.A. HUDSON

Drug Information Centre, Clinical Sciences Building, Leicester Royal Infirmary, Leicester

A. McBURNEY

Department of Clinical Pharmacology, Groby Road Hospital, Leicester

The plasma and breast milk were sampled from a woman who was breastfeeding whilst taking disopyramide (200 mg three times daily). Paired samples taken on the fifth to eighth day of treatment showed that disopyramide was present in breast milk in a similar concentration to plasma (mean  $\pm$  s.d. milk: plasma ratio  $0.9 \pm 0.17$ ). The estimated dose likely to be ingested by an infant is less than  $2 \text{ mg kg}^{-1} \text{ day}^{-1}$ . The active *N*-monodesalkyl metabolite of disopyramide (NMD) although present in plasma in much smaller concentrations than the parent compound, was excreted in breast milk (mean  $\pm$  s.d. milk: plasma ratio  $5.6 \pm 2.9$ ) in concentrations similar to those of disopyramide. The pharmacological and toxicological properties of the disopyramide metabolite need to be considered when assessing likely effects on the infant. No adverse effects were noted in the infant in this case. Maternal plasma and breast milk were sampled again along with infant plasma after 28 days. Disopyramide and NMD were undetectable in the infant's serum. No evidence was found to indicate that the concentrations of disopyramide or NMD in breast milk might be sufficient to pose a definite risk to the infant. Whenever disopyramide is prescribed in a breast feeding mother, close observation of the baby and measurement of both disopyramide and its active metabolite NMD in breast milk or infant plasma is recommended, pending further investigation.

### Introduction

Antidysrhythmic drugs may sometimes need to be prescribed during and after pregnancy. Although data on excretion in breast milk is now available for several  $\beta$ -adrenoceptor-blockers (Bauer *et al.*, 1979; Devlin *et al.*, 1981; Liedholm *et al.*, 1981) and mexiletine (Lewis *et al.*, 1981), information on other antidysrhythmic drugs is sparse. We have found it necessary to estimate disopyramide and its monodesalkyl metabolite in the breast milk of a young mother who has come under our care recently.

### Methods

A 25 year old West Indian woman (gravida 5, para 5) of 34 weeks gestation gave a history of lassitude and complained of bouts of exertional chest pain, mild dyspnoea and occasional palpitations. On examination she had an irregular pulse with marked pulse deficit, clinical cardiomegaly but no evidence of congestive cardiac failure at rest. A 24 h ECG indi-

cated sinus rhythm, multifocal ventricular ectopic beats with very frequent runs of supraventricular and ventricular tachycardia. Chest X-ray and echocardiogram showed an enlarged left ventricle with low ejection fraction but normal cardiac valves. A diagnosis of diffuse cardiomyopathy was made and oral disopyramide (200 mg three times daily at 06.00 h, 14.00 and 22.00 h) was commenced on 22.10.81, to control the arrhythmia in anticipation of her going into labour. On the next day the patient delivered a normal healthy infant uneventfully.

Four paired maternal plasma and breast milk samples (drawn prior to the midday dose) and five separate breast milk samples (drawn at the midpoint and end of the dosing interval) were taken on the fifth to the eighth day of treatment. Samples of breast milk (10 ml) were taken using a standard pump (Egnell) before suckling of the infant commenced and thereafter between feeds.

Further paired maternal samples (drawn immediately prior to and 1 h after the midday dose) were

taken along with an infant blood sample at outpatient follow up after 4 weeks of treatment.

Disopyramide and its major active metabolite, *N*-monodesalkyl disopyramide (NMD), were measured using a high pressure liquid chromatographic method (Lima, 1979) with extraction using chloroform containing *p*-chlorodisopyramide (10 mg/l) as internal standard. The eluent for chromatography was 40% acetonitrile in 0.2 M acetate buffer at pH 3.7.

## Results

The results are shown in Table 1. The plasma concentration of disopyramide in the baby on day 28 was found to be 0.5 mg/l. The concentration of NMD was not detectable. The infant showed no symptoms to indicate any effect of disopyramide.

## Discussion

Previous published information on the transfer of disopyramide into breast milk is limited to measurements in rats (Karim *et al.*, 1978) in which the milk:plasma (M:P) ratio was found to vary from 1–3. The radiolabelling technique used for drug assay in this study would also have measured disopyramide metabolites. In addition the metabolism of disopyramide in the rat is known to differ qualitatively from that in humans and therefore the relevance of the animal studies is dubious.

We have found disopyramide to be present in human breast milk in similar concentrations to that in plasma (mean  $\pm$  s.d. milk:plasma ratio  $0.9 \pm 0.17$ ). We estimate the infant would receive a dose of about 4 mg/day (or less than 2 mg kg<sup>-1</sup> day<sup>-1</sup>) assuming an average maternal plasma concentration of 4 mg/l and

a maximum daily milk intake of 1 litre. For adults the minimum recommended dose of disopyramide is 5.7 mg kg<sup>-1</sup> day<sup>-1</sup>. Although there is little experience of its use in children, proportionately larger doses of disopyramide in excess of 15 mg kg<sup>-1</sup> day<sup>-1</sup> have been reported to be necessary in newborn infants, in order to achieve plasma concentrations in the therapeutic range of 2–5 mg/l (Holt *et al.*, 1979).

In contrast to the parent compound, measurement of the excretion of the metabolite NMD in breast milk (Table 1) showed a tendency for it to accumulate (mean milk:plasma ratio 5.6). In fact the concentration of the metabolite in breast milk was similar to that of disopyramide. The pharmacological contribution of NMD needs to be considered both from the point of view of efficacy and toxicity. Although it has only 25% of the antidysrhythmic activity of disopyramide (Grant *et al.*, 1978) the only published information suggests that NMD is twenty-four times more potent in terms of anticholinergic activity in the guinea pig isolated ileum (Baines *et al.*, 1976). However, our own unpublished observations, using *in vitro* displacement of radioactive ligand binding to cerebral muscarinic receptors, suggest that NMD and parent drug are equipotent in this system. Even so the contribution of NMD to the overall anticholinergic activity of disopyramide and possible infant toxicity must be considered in view of the enhanced breast milk excretion of the metabolite.

Since in this case NMD was undetectable in the infant's serum, our findings provide no evidence that the presence in breast milk of disopyramide or its active metabolite is sufficient to pose a definite risk to a suckling infant. We would however advise close observation of the baby with measurement of both compounds in maternal breast milk or infant plasma, pending further investigation.

Reprint requests should be addressed to SAH.

**Table 1** Breast milk and blood concentrations (mg/l) of disopyramide and *N*-monodesalkyl disopyramide (NMD).

Day of therapy	Plasma		Breast milk		Milk:plasma	
	disopyramide	NMD	disopyramide	NMD	disopyramide	NMD
	(mg/l)		(mg/l)			
5	2.9	0.4	2.6	2.2	0.9	5.5
6			5.1	3.6		
	3.9	0.5	4.1	1.8	1.0	3.6
			3.4	3.3		
7			5.7	3.5		
	4.0	0.6	3.3	3.2	0.8	5.3
			3.3	4.8		
8			4.3	2.8		
	3.6	0.5	4.0	4.4	1.1	8.8
28	4.1	0.5	2.9	2.5	0.7	5.0
	5.4	0.5	4.2	2.9	0.8	5.8
Mean $\pm$ s.d.	4.0	0.5	3.9	3.2	0.9 $\pm 0.17$	5.6 $\pm 2.9$

## References

- BAINES, M.W., DAVIES, J.E., KELLETT, D.N. & MUNT, P.L. (1976). Some pharmacological effects of disopyramide and a metabolite. *J. int. med. Res.*, **4**, (Suppl 1), 5-7.
- BAUER, J.H., PAPE, B., ZAJICEK, J. & GROSHONG, E. (1979). Propranolol in human plasma and breast milk. *Am. J. Cardiol.*, **43**, 860-862.
- DEVLIN, R.G., DUCHIN, K.L. & FLEISS, P.M. (1981). Nadolol in human serum and breast milk. *Br. J. clin. Pharmacol.*, **12**, 393-396.
- GRANT, A.M., MARSHALL, R.J. & ANKIER, S.I. (1978). Some effects of disopyramide and its *N*-dealkylated metabolite on isolated nerve and cardiac muscle. *Eur. J. Pharmacol.*, **49**, 389-394.
- HOLT, D.W., WALSH, A.C., CURRY, P.V. & TYNAN, M. (1979). Paediatric use of mexiletine and disopyramide. *Br. med. J.*, **2**, 1476-1477.
- KARIM, A., COOK, C. & CAMPION, J. (1978). Placental and milk transfer of disopyramide and metabolites. *Drug. Metab. Dispos.*, **6**, 340-341.
- LEWIS, A.M., JOHNSTON, A., PATEL, L. & TURNER, P. (1981). Mexiletine in human blood and breast milk. *Postgrad. med. J.*, **57**, 546-547.
- LIEDHOLM, H., MELANDER, A., BITZEN, P.O., HELM, G., LONNERHOLM, G., MATTIASSON, I., NILSSON, B. & WAHLIN-BOLL, E. (1981). Accumulation of atenolol and metoprolol in human breast milk. *Eur. J. clin. Pharmacol.*, **20**, 229-231.
- LIMA, J.J. (1979). Liquid chromatographic analysis of disopyramide and its mono-*N*-dealkylated metabolite. *Clin. Chem.*, **25**, 405-408.

(Received March 6, 1982,  
accepted May 6, 1982)