

is metabolized and  $F_H(m)$  is the systemic availability of the metabolite.

In conclusion, MBRT( $m$ ) is a useful model-independent characteristic giving information concerning the metabolite concentration-time profile (and consequently to some extent also concerning the duration of the effect of an active metabolite). If additionally  $F_H(m)$  and  $f_m$  are known the basic pharmacokinetic parameters of the metabolite can be estimated from metabolite and drug concentration-time curves following drug administration using equations (5), (9) and (3).

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## Excretion of disopyramide in human breast milk

Data concerning the transfer of disopyramide to human breast milk are sparse and only a single case report of a study on one mother and her infant has been located (Barnett *et al.*, 1982). Presented here is further data on the excretion of disopyramide in breast milk and its transfer to the newborn infant.

The patient, a 25 year old Caucasian woman, had been taking disopyramide 100 mg 5 times daily throughout her pregnancy. Two days after delivery of a normal female infant, and approximately 2 h after a dose, a paired sample of breast milk and maternal serum were collected for estimation of disopyramide by EMIT (Syva, Palo Alto) method. Breast milk was centrifuged and the aqueous phase retained for assay of disopyramide. Facilities for measuring the *N*-monodesalkyl metabolite were not available. The serum level of disopyramide was 10.3  $\mu\text{mol/l}$  and that in breast milk 4.0  $\mu\text{mol/l}$  giving a milk:serum ratio of 0.4. Two weeks later, a further pair of samples was obtained and in

addition infant serum was collected. Samples were collected approximately 3 h after a dose and immediately prior to an infant feed. Disopyramide levels were: maternal serum 11.5  $\mu\text{mol/l}$  and breast milk 5.0  $\mu\text{mol/l}$ . No disopyramide was detected in the infant's serum (limit of accuracy of method 1.5  $\mu\text{mol/l}$ ).

The milk:serum ratio is lower in this case than that previously reported (Barnett *et al.*, 1982), 0.4 vs 0.9 despite similar plasma/serum concentrations. This discrepancy may simply be a reflection of interindividual variability or may be related to determination of disopyramide in the aqueous fraction of the milk with resulting loss of fat soluble drug in the lipid portion. If the latter is the case, the amount of drug present in whole milk has been underestimated. However, no significant concentrations of disopyramide were detected in the infant's serum and no evidence of adverse effects were evident on clinical examination.

On the present data, it is estimated that the

infant would receive approximately 1.5 mg of disopyramide per day assuming a generous intake of 1 l of milk. Even taking into account the two fold variability in breast milk levels of disopyramide reported by Barnett *et al.* (1980), the maximum amount of drug transmitted to the infant would be 3 mg/day (0.6% of the maternal dose).

The manufacturer's product information recommends, on the basis of animal data showing concentration of the drug in breast milk of rats, (Karim *et al.*, 1978) that breast feeding be discontinued if the mother is receiving disopyramide. The present data are in general agreement with that of Barnett *et al.* (1982) in demonstrating that disopyramide is not concentrated in human breast milk and that infants so exposed

are unlikely to be adversely affected by the relatively small quantities of drug ingested. However, until further data are gathered it seems prudent to observe these infants closely for adverse effects, particularly those relating to the anticholinergic action of disopyramide and its *N*-monodesalkyl metabolite in view of the reported increased susceptibility of infants to anticholinergic drugs (Wilson, 1981).

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## Mexiletine clearance during peritoneal dialysis

The pharmacokinetics of mexiletine in patients undergoing peritoneal dialysis have been the subject of only one case report (Jones *et al.*, 1983). The effect of haemodialysis on mexiletine pharmacokinetics is unknown. Renal impairment itself has little effect on the pharmacokinetics of mexiletine until the creatinine clearance is reduced to less than 10 ml/min, at which point the total body clearance is slightly reduced from the 6-13 ml min<sup>-1</sup> kg<sup>-1</sup> noted in normal volunteers and patients with normal renal function (Haselbarth *et al.*, 1981; Campbell *et al.*, 1978) to 2.4-9.9 ml min<sup>-1</sup> kg<sup>-1</sup> (El Allaf *et al.*, 1982). A patient requiring mexiletine therapy while admitted to the intensive care unit provided the opportunity to assess the peritoneal clearance of mexiletine.

A 70 year old Caucasian male with a past history of congestive cardiomyopathy, mitral regurgitation, hypertension, repeated bouts of peritonitis, and chronic renal failure treated with continuous ambulatory peritoneal dialysis (CAPD) was admitted from the ward into the intensive care unit after resuscitation from a

cardiopulmonary arrest. The arrest was thought to be secondary to myocardial ischaemia and the hypotension secondary to sublingual nitroglycerin use. The course was complicated by congestive heart failure characterized by very high pulmonary capillary wedge pressures (30-40 mm Hg) and exquisite sensitivity to vasodilator therapy. As well, multifocal premature ventricular contractions (PVC) developed which were treated with lignocaine. Dialysis therapy consisted of 6 hourly 2 l exchanges with 1.5 and 4.25% dextrose solutions (Dianeal, Baxter-Travenol). The number of exchanges of a given dextrose concentration instilled daily depended on the patient's fluid status. There was no evidence of peritonitis. As PVC continued after tapering off the lignocaine infusion, it was decided to commence long-term mexiletine therapy. Coincident with the beginning of a dialysate instillation, 200 mg of mexiletine (Boehringer-Ingelheim) was given orally. Serial serum samples were collected over the 8 h dosing interval. Urine was not produced over this period of time. Dialysate was collected over the 6 h