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Letters to the Editor

Pilsicainide in breast milk from a mother: comparison with disopyramide and propafenone

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Information about the transfer of antiarrhythmic drugs into milk is available. However, results for the same drug sometimes vary. This variation may be due to factors such as interpatient variation of drug transfer or the small number of patients in the studies. Equations are useful for predicting drug transfer into milk [1]. Pilsicainide is a new class I antiarrhythmic drug used in Japan. We collected serial specimens of plasma and milk after a single dose of three different antiarrhythmic drugs, including pilsicainide, in a healthy mother. We also compared the results with an equation for predicting the milk/plasma ratio.

One healthy nursing mother (one of the authors, M.W.; body weight 56 kg) took a single oral dose of either pilsicainide (50 mg), disopyramide (100 mg) or propafenone (150 mg) after a 12-h fast. The wash-out period between each dose was 4 weeks and the order of the section was randomly chosen. She was prohibited from breast feeding on trial days. Blood and milk samples were collected at 1, 2, 3, 4, 6, and 12 h after each dosing. Breast milk samples were collected by manual expression and milk pH was measured anaerobically. For sampling milk, breasts were emptied of milk at each time point and a stirred aliquot was taken for analysis. Protein binding of each drug was measured after microultrafiltration. Concentrations of pilsicainide, propafenone, 5-(OH)propafenone and disopyramide were measured using high-performance liquid chromatography [2, 3] or enzyme immunoassay [4]. The detection limit was 0.06 μg ml^{-1}, 10 ng ml^{-1}, 10 ng ml^{-1}, and 0.07 μg ml^{-1}, for pilsicainide, propafenone, 5-(OH)propafenone and disopyramide, respectively. The milk/plasma ratio of each drug (M/P_{obs}) was calculated by the ratio of $AUC_{0-12\,h}$ for milk and plasma, obtained by the trapezoidal method. Pharmacokinetic parameters of pilsicainide after a single oral administration were estimated using the least square method applied to a one-compartment open model with first-order absorption and elimination. The maximum and minimum serum concentrations of pilsicainide at steady state were calculated by the estimated pharmacokinetic parameters using computer software. The body weight-adjusted relative infant dose of the drug was calculated from the assumption that a baby takes 150 ml kg^{-1} day^{-1} of milk. Finally, we estimated the M/P ratio (M/P_{pred}) according to the previously reported equations of Begg [1], and compared the results with actual M/P_{obs}. The Ethics Committee of the Medical School approved the protocol.

The pilsicainide concentration in milk was higher than that in plasma at each observation point, whereas disopyramide and propafenone concentrations in milk were lower than those in plasma (Table 1). Estimated C_{max}/C_{min} at steady state, M/P_{obs}, protein binding, milk pH, octanol/water partition coefficient at pH 7.2 and pKa used for the prediction are also shown.

The value of M/P for disopyramide varies widely (from 0.4 to 0.9) among reports [5–7]. Because the protein binding ratio of disopyramide is nonlinear with respect to concentration [8], this difference might be due to the different concentrations of the drugs used in these reports. The M/P_{obs} of pilsicainide is highest among the three drugs and concentrations were detected at 12 h in both plasma and milk after a single dosing. This is the first report on the M/P ratio of pilsicainide. $AUC_{0-12\,h}$ of pilsicainide in milk was 4.7 μg h^{-1} ml^{-1}. If we assume that a baby takes 150 ml kg^{-1} day^{-1} of milk, the estimated amount of ingested drug is 0.05875 mg, which means that the body weight-adjusted relative infant dose is 7% (Table 1). Because 10% is the notionally accepted cut-off for an average drug, this value for pilsicainide is just within the accepted range. The M/P_{obs} for propafenone was lowest among the three in this study. There is one report for propafenone [9] and the value is

Table 1
Pharmacokinetic profiles of three antiarrhythmic drugs

	Concentration												Estimated C_{max}/C_{min} at steady state		$AUC_{0-12\,h}/AUC_{0-\infty}$		pH of milk	Protein binding ratio (%)	pKa*	Octanol/ water partition coefficient*	M/P obs†	M/P pred‡	Relative infant dose (%)
	1 h		2 h		3 h		4 h		6 h		12 h												
	M	P	M	P	M	P	M	P	M	P	M	P	M	P	M	P							
Pilsicainide (μg ml^{-1})	0.84	0.42	0.67	0.41	0.55	0.31	0.48	0.27	0.36	0.21	0.16	0.10	1.19/0.40	0.65/0.24	4.70/5.25 (μg h^{-1} ml^{-1})	2.70/2.98	7.16	12.6	10.2	1.76	1.75	1.91	7
F-pilsicainide (μg ml^{-1})		0.37		0.35		0.28		0.24		0.18		0.08											
Disopyramide (μg ml^{-1})	0.47	1.35	0.65	1.41	0.64	1.46	0.64	1.41	0.44	1.03	0.11	0.45	0.89/0.37	2.47/1.21	4.80/5.10 (μg h^{-1} ml^{-1})	11.80/12.21	6.90	81.4	8.36	0.66	0.41	0.79	3
F-disopyramide (μg ml^{-1})		0.26		0.28		0.26		0.25		0.18		0.07											
PROP (ng ml^{-1})	21.9	51.6	37.4	124.0	27.0	82.0	15.5	54.7	ND	26.3	ND	ND	39.5/0.58	118.2/4.3	109.6/109.8 (ng h^{-1} ml^{-1})	444.8/422.46	6.97	82.7*	9.56	68.3	0.25	0.81	0.1
5-OH-PROP (ng ml^{-1})	2.9	49.6	102.0	89.5	73.8	66.7	45.4	41.5	19.8	26.7	ND	12.9											

*M, Milk; P, plasma; F, free; PROP, propafenone. *Information from manufacturers. †Calculated from $AUC_{0-12\,h}$ milk/$AUC_{0-12\,h}$ plasma. ‡Calculated from Ref. 2. ln M/P = –0.09 + 2.54 ln (Mu/Pu) + 0.79 ln (fu,p) + 0.46 ln K.*

comparable to that reported in this study. The equation of Begg gave a close M/P_{pred} for pilsicainide. However, since there was only one subject in this study, further studies should be conducted with a larger number of subjects to confirm these findings. We did not collect samples more than 12 h after dosing, which is a limitation of this study. $AUC_{0-12\,h}$ was between 89 and 100% of AUC_{0-8} for the three drugs. We did not measure N-monodealkylated disopyramide, which has higher cholinergic activity than the parent compound, in this study. Accumulation of this metabolite into breast milk is reported [5], which might also have occurred in our study. Although the relative infant dose for disopyramide is low, careful monitoring is needed in the clinical setting.

In conclusion, we report here for the first time the drug transfer of pilsicainide after a single dosing in a healthy mother. We also evaluated transfer of disopyramide and propafenone in an identical mother. Begg's equation is effective for predicating the M/P-value, especially for pilsicainide. These observations may be useful for the treatment of arrhythmia in patients who are breast feeding.

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