BIOPHARMACEUTICS & DRUG DISPOSITION, VOL. 4, 299–301 (1983)

LEVELS OF THE BETA-BLOCKERS ATENOLOL AND PROPRANOLOL IN THE BREAST MILK OF WOMEN TREATED FOR HYPERTENSION IN PREGNANCY

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INTRODUCTION

The excretion of drugs in human milk is a complex process which is poorly understood at present. It is said that physiochemical properties may be important. The beta-blockers constitute a group of chemically similar compounds which are weak bases, but differ in lipid solubility and protein binding. They are increasingly used in the treatment of hypertension in pregnancy and may then be given to lactating women. We are studying this group of compounds to assess possible risks to the neonate, and to weigh the importance of these physical properties of drugs on breast milk excretion. We present some preliminary findings comparing atenolol, which has low lipid solubility and protein binding, with propranolol which is both highly lipid-soluble and protein-bound.

PATIENTS AND METHODS

Ten women received atenolol 100 mg daily or propranolol 40 mg twice daily orally during the puerperium. Samples of venous blood and breast milk were taken at 2 h after the morning dose. The blood and milk concentration of atenolol were estimated by the gas–liquid chromatographic method of Scales and Copsey.[1] The blood and milk concentrations of propranolol were measured by the gas–liquid chromatographic method of McAinsh *et al.*[2]

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0142–2782/83/030299–03$01.00

Received 15 January 1983

RESULTS

The pH of the milk samples ranged from 7·33 to 7·82 (mean 7·54, S.D. ±0·19). The systemic blood and breast milk levels of the drugs are shown in Table 1. The mean blood/milk ratios were 1·3 : 1 for atenolol and 2·0 : 1 for propranolol. None of the babies showed any clinical signs of beta-blockade.

Table 1. Breast milk and systemic blood levels of atenolol (A) and propranolol (P) (ng ml^{-1}) 2 h after oral dosing with 100 mg of atenolol and 40 mg of propranolol

Patient	Drug	Concentration (ng ml^{-1}) Milk	Blood	Ratio
1	A	380	860	2·3
2	A	1040	640	0·6
3	A	440	760	1·7
4	A	530	450	0·8
5	A	760	850	1·1
Mean		630	712	1·3
S.D.		271	171	0·7
S.E.		121	77	0·3
6	P	35	95	2·7
7	P	36	83	2·3
8	P	16	31	1·9
9	P	35	36	1·0
10	P	14	27	1·9
Mean		27	54	2·0
S.D.		11	32	0·6
S.E.		5	14	0·3

DISCUSSION

Assuming a milk intake by the neonate of 500 ml per day, the maximum daily dose of atenolol received by the baby would be approximately 0·3 mg per day, and of propranolol 0·01 mg per day.

Atenolol seems to be distributed between blood and milk in approximately equal proportions whereas propranolol is found at about half of its blood level in milk. The levels of atenolol are considerably lower than those found by Liedholm *et al.*[3] Our levels were measured when maximum maternal blood concentrations would be expected. There seems to be considerable variation in milk levels of atenolol, which may be explained by maternal factors rather than physicochemical properties of the drug. This observation is confirmed in a further study using a new method of estimation of the drug in very small milk samples, developed at Guy's Hospital Poisons Unit and using high-performance liquid chromatography (HPLC).[4] This method allows more

sampling, and early results indicate wide variation both between and within patients in levels of atenolol. The plasma/milk ratio varies by as much as 12-fold within the same patient and 40-fold between patients.

It may be that factors in the milk itself, such as the fat and protein content, may influence levels of drugs. These vary considerably during the first few days of lactation. The time of collection of the milk samples in relation to a feed may also affect levels.

It is proposed to use the HPLC method to compared the excretion of a range of beta-blockers in milk in the hope of disentangling, at least in part, the effects of these various factors on the secretion of drugs in human milk. Meanwhile, although it would appear that the drugs studied may be used safely during lactation, we conclude that the choice of drugs used in lactating women should be made on the basis of clinical observation.

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