Following labetalol administration there was a significant increase in plasma glucose concentration with a peak at 10 min after which the concentration declined to baseline levels by 45 min. No increase occurred in plasma glucose concentrations following hydrallazine, phentolamine or placebo (Table 1).

It is unlikely that the increase in plasma glucose concentration that followed administration of labetalol is due to its α- and β- antagonist activity. β-adrenoceptor blocking drugs inhibit glycogenolysis and may precipitate hypoglycaemia. α-adrenoceptor blockade by phentolamine in the present experiment failed to increase plasma glucose during the period of observation. The increase in plasma glucose following labetalol was not secondary to the hypotensive effect of the drug as it did not occur when the blood pressure was reduced to the same extent with hydrallazine. It is suggested that labetalol may cause temporary increase in plasma glucose by promoting glucogenolysis by β_2-adrenoceptor agonist action.

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METOPROLOL EXCRETION INTO BREAST MILK

Pharmacokinetic studies on metoprolol have shown that the drug is extensively distributed to various tissues and that only 1 to 2 % of the total amount of the drug in the body is localized in the blood (Regårdh, Borg, Johansson, Johnsson & Palmer, 1974). Metoprolol must therefore readily cross different kinds of biological membranes including the placenta; it was recently shown that the concentration of metroprolol in maternal and umbilical cord blood is about the same (Sandström, 1978).

It might be anticipated that metoprolol being a weak base ($pk_a = 9.7$) of moderate lipid solubility and only bound to about 10% to human serum proteins will diffuse through the mammary gland epithelium and become concentrated to some extent in the breast milk, which usually has a somewhat lower pH value than the plasma (Rasmussen, 1958, 1959). However, no information is yet available to answer the question whether the concentration of metoprolol in milk is high enough to cause significant β-adrenoceptor blockade in the breast-fed child.

Breast milk and blood were simultaneously collected from nine nursing mothers who had been treated with varying doses of metoprolol during pregnancy. The treatment period varied from about 1 week up to the whole gestation period. The concentration of metoprolol in the breast milk and in the plasma was assayed by a specific gaschromatographic method (Ervik, 1975). In order to avoid interference from the fat in the breast milk, the initial alkaline extract was extracted with 0.01 M H_2SO_4 and thereafter reextracted into the organic phase prior to evaporation and TFA-acylation.

The individual data of the patients studied are summarized in Table 1. The concentration of metoprolol in the plasma of the nursing mothers was in the same range as previously observed at corresponding sampling times in healthy volunteers given the same dose of metoprolol (Johnsson, Jordö, Lundborg, Regardh & Ronn, 1980).

On average, the concentration of metoprolol in breast milk was about 3.5 times higher than in the plasma. However, during the first 1.5 to 3 h after administration, i.e., usually during the absorption phase and close to the time of peaking of the plasma concentration *v.* time curve, the breast milk contained proportionally less metoprolol than when the samples were collected later in the dosage interval. Whether

Table 1 Individual metoprolol dosages, time of sample collection in relation to drug intake and the concentration of metoprolol in plasma and breast milk

Subject	*Dosage*	*Sampling time (h after dosage)*	C_{plasma} ($nmol\ l^{-1}$)	$C_{breast\ milk}$ ($nmol\ l^{-1}$)	C_{breast}/C_{plasma} *milk*
1	100 mg × 2	3	556	1690	3.0
2	100 mg × 2	8	182	740	4.1
3	50 mg × 2	4.5	425	1560	3.7
4	50 mg × 2	1.5	132	332	2.5
5	50 mg × 2	12	4	19	4.8
6	100 mg × 2	5	225	857	3.8
7	100 mg × 2	2	128	399	3.1
8	100 mg × 2	6	24	114	4.8
9	100 mg × 2	5	190	694	3.7
Mean ± s.e. mean					3.72 ± 0.26

this is due to individual variation in the breast milk-plasma concentration ratio or to a relatively slow partitioning of metoprolol between the breast milk and the plasma cannot be decided from the present data. An increase in the breast milk-plasma partition ratio of metoprolol from 3 to 5 during the dosage interval would, however, only result in a slightly longer elimination half-life of the drug in the breast milk than in the plasma, and would not lead to any further accumulation of the drug in the breast milk.

According to previous studies (Johnsson *et al.*, 1980; von Bahr, Collste, Frisk-Holmberg, Haglund, Jorfelt, Orme, Ostman & Sjöqvist, 1976) a daily dose of 200 mg metoprolol causes a mean steady state concentration in the plasma of about 75 ng ml^{-1}. Using the concentration ratio obtained in the present study the mean steady state concentration in the breast milk would be about 280 ng ml^{-1}. An infant consuming 1 litre of breast milk per day would thus receive an average dose of metoprolol of approximately 0.07 mg kg^{-1} day^{-1}, assumming a body weight of 4 kg. This dose is 20 to 40 times less than the normal daily dose for a hypertensive patient.

It seems unlikely, therefore, that the amount of metoprolol that can be ingested in milk would induce any adverse reactions in the breast-fed child unless its liver function was severely under-developed. This possibility is being studied at present.

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