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Anti-hypertensive therapy with propranolol during pregnancy and lactation

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Summary

A hypertensive woman was treated throughout pregnancy with propranolol 40 mg daily without complication. At delivery the umbilical cord plasma concentration was similar to that in the maternal venous plasma. Milk:plasma ratios were less than 1, although a higher ratio would be predicted. Estimated daily intake of propranolol in breast milk by the infant was about 3 μg. There appears to be no reason to advise women receiving propranolol to avoid breast feeding.

Introduction

Propranolol has been administered to patients with a variety of conditions associated with pregnancy such as: hypertension (Tcherdakoff *et al.*, 1978; Eliahou *et al.*, 1978), hyperthyroidism (Bullock, Harris and Young, 1975; Burrow, 1978), cardiac arrhythmias (Schroeder and Harrison, 1971; Levitan and Manion, 1973), hypertrophic obstructive cardiomyopathy (Turner, Oakley and Dixon, 1968; Datta *et al.*, 1978) and fetal tachycardia in diabetic pregnancy (Teuscher *et al.*, 1978).

Its use has been questioned for 2 main reasons: its possible stimulant action on uterine muscle due to β^2-adrenoceptor blockade (Pose, Cibils and Zuspan, 1962; Wansbrough, Nakanishi and Wood, 1968) and its pharmacological effects on the fetus (Habib and McCarthy, 1977; Cottrill *et al.*, 1977). The main effects seen in the neonate are low birthweight (Reed *et al.*, 1974; Oakley *et al.*, 1979) possibly owing to inadequate perfusion of the fetal side of the placenta (Barden and Stander, 1968), hypoglycaemia and bradycardia (Habib and McCarthy, 1977; Cottrill *et al.*, 1977), and respiratory depression (Tunstall, 1969). However, other workers have given β-adrenoceptor antagonists to pregnant women with no ill effects on mother or child (Tcherdakoff *et al.*, 1978; Gallery *et al.*, 1978; Dubois *et al.*, 1978). Gallery *et al.* (1978) found a significant inverse relationship between blood pressure in untreated hypertensive subjects in late pregnancy, and birthweight which was reversed in 19 patients treated with oxprenolol. In 3 patients, side effects of propranolol were seen with daily doses greater than 160 mg (Cottrill *et al.*, 1977; Gladstone, Hordof and Gersony, 1975); however, they are also seen, less frequently, with lower daily doses (Habib and McCarthy, 1977).

Cottrill *et al.* (1977) observed in the neonate an increase in the plasma propranolol concentration from about 30 ng/ml at birth to 90 ng/ml by 4 hr. Their suggestion that this could be due to a redistribution of the drug, perhaps in combination with defective elimination, was interesting and worth further investigation.

Case report

The authors have studied a hypertensive patient who took propranolol 20 mg twice daily throughout pregnancy. At delivery, samples of maternal venous and umbilical cord blood were taken for the measurement of propranolol concentrations in plasma. Neonatal venous plasma concentrations of propranolol were followed for 4 hr after birth, and the progress of the neonate during the first week after birth was recorded.

A 28-year-old patient, gravida 1, para 0, who had regularly attended the hypertension clinic at St Bartholomew's Hospital before pregnancy, continued on oral propranolol throughout pregnancy. Her blood pressure at the last visit to the clinic at 39 weeks was 115/85 mmHg. After admission to hospital the patient was taking, in addition to propranolol, mefenamic acid (Ponstan) capsules 250 mg – one or 2 daily; magnesium trisilicate mixture – 10 ml/2 hr; nitrazepam 5 mg – one at night; dextropropoxyphene 32·5 mg and paracetamol 325 mg (Distalgesic) – one or 2/6 hr (after delivery); ferrous sulphate and folic acid (Fe Folic) – one daily.

The last dose of propranolol was given 3·15 hr before delivery. At 00·15 hr (day 1) the patient underwent a spontaneous vaginal delivery of a 3420 g female with Apgar scores of 8 at one min and 9 at 5 min. At delivery the maternal blood pressure was 125/80 mmHg, and at this time a 10-ml sample of

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venous blood from the mother and a 10-ml bood sample from the maternal end of the umbilical cord were taken into lithium-heparin. Four blood samples of approximately 2 ml each were collected from the neonate at 0·5, 1, 2 and 4 hr after delivery, the 0·5-hr sample through a small butterfly cannula in the antecubital vein and subsequent samples by heel prick. Plasma was separated and stored at −20°C until assayed by gas-liquid chromatography (McAinsh *et al.*, 1978). The lower limit of sensitivity of the method was a concentration in plasma of 8 ng/ml. The results are given in Table 1.

The patient was reluctant to give more blood, but it was possible to obtain 2 more specimens of breast milk at different times after dosing to estimate how much propranolol the infant was receiving per day. All samples were taken at the end of feeding. The blood samples were treated as above and the concentrations of propranolol in plasma and in whole milk were measured by the method described by McAinsh *et al.* (1978). The lower limit of sensitivity of the assay in milk was 2 ng/ml. The results are also shown in Table 1.

For the estimation of the daily intake of drug by the neonate, both the concentration of propranolol in milk and the volume of milk taken per day must be known. The infant was therefore weighed before and after each feed over a 24-hr period. Assuming a mean concentration of 10 ng/ml in milk, the intake of propranolol by the neonate on the fifth day after birth was estimated to be approximately 3 μg.

The apex heart rate of the infant receiving propranolol was compared to that in one female and 2 male infants of similar ages and weights at 6 p.m. and 6 a.m. on days 4 and 5 respectively, and with 5 other female infants of similar ages and weights at the same times on days 6 and 7. There was no difference between the heart rate of the infant receiving propranolol and that of the other infants over the period of investigation. The heart rate of the infant receiving propranolol was 136 and 144 beats/min on days 4 and 5 respectively, and the mean ±s.d. of the control infants was 120·7±3·1 and 133·3±9·9 at the same times. On days 6 and 7 the heart rate of the baby being investigated was 136 and 140 beats/min respectively, and the mean of the control infants was 140·0±7·6 and 140·0±8·9.

Discussion

In this patient treated with a low dose of propranolol throughout pregnancy, there were no detectable adverse effects on mother or infant. This is consistent with the view that in patients with hypertension, in the absence of other complictions, taking <160 mg/day of propranolol, few maternal or neonatal adverse effects are seen (Tcherdakoff *et al.*, 1978; Gregoric *et al.*, 1978).

There is no doubt that propranolol crosses the placenta, as plasma concentrations have been reported in several neonates (Habib and McCarthy, 1977; Cottrill *et al.*, 1977; Langer *et al.*, 1974; Teuscher *et al.*, 1978). Information on the pharmacokinetics of drugs in the newborn is scant and often restricted to single determinations of drug concentrations in maternal and neonatal blood samples at delivery. Langer *et al.*, (1974) and Teuscher *et al.* (1978) found that the propranolol concentration in neonatal blood and plasma was one fifth of the maternal concentration at delivery and also 2·5 hr later in the case of the latter workers. A slightly higher concentration in umbilical cord plasma (arterial and venous) than in maternal plasma was reported by Cottrill *et al.* (1977) which is similar to the present results. Teuscher *et al.* (1978) found that the plasma drug concentration in the neonate fell from 26 ng/ml at delivery to 18·5 ng/ml 2·5 hr later. This decline was similar to that in the present study where the neonatal plasma concentration fell from 14 ng/ml at birth to 11 ng/ml by 0·5 hr, and to less than 8 ng/ml by one hr.

TABLE 1. Plasma concentration of propranolol in mother and umbilical cord at time of delivery, and in the neonate 0·5, 1, 2 and 4 hr after birth. Propranolol concentration in breast milk and simultaneous samples of maternal blood are shown

Day sample taken	Time after last dose (hr)	Propranolol concentration (ng/ml)			
		Mother	Plasma Cord	Infant	Milk
1	3·25	19	14		
1	3·75			11 (0·5 hr)	
1	4·25			ND (1 hr)	
1	5·25			ND (2 hr)	
1	7·35			ND (4 hr)	
3	1–2				20
4	2·25	17			4
5	12				ND
6	3·25	16			11

ND = below the limit of detection—8 ng/ml for plasma, 2 ng/ml for milk.

In the present study, the concentration ratio of propranolol in milk to that in plasma was 0·24, 2·25 hr after the last dose, and 0·69, 3·25 hr after the last dose of propranolol. These ratios were similar to those reported by Bauer *et al.* (1979) and Levitan and Manion (1973). Karlberg, Lundberg and Aberg (1974) found milk : plasma ratios of propranolol concentration of approximately 1 after various single oral doses in 2 nursing mothers. Human milk is at pH 6·5 to 7·0; therefore, for a weak base such as propranolol (p*K*a 9·45), a milk - plasma ratio >1 would be expected, binding to protein and lipids in milk would be expected further to increase the ratio. Karlberg *et al.* (1974) suggested that the lower ratios usually seen may be a result of propranolol in milk equilibrating with that free in plasma during the time of increasing plasma concentrations, i.e. during the time interval preceding peak plasma concentrations when most blood samples were taken. However, propranolol is such a lipid-soluble drug that equilibrium across a lipid membrane would be expected to occur rapidly. Furthermore, in a patient taking propranolol 40 mg 4 times daily, both plasma and milk concentrations were found to peak at 3 hr after the last dose of drug, and both declined thereafter (Bauer *et al.*, 1979). It is, therefore not known why the milk : plasma ratio of propranolol concentration is <1.

The estimated intake of propranolol was 3 μg daily by the infant in the present study. Bauer *et al.* (1979) estimated, using the peak propranolol concentration after dosage at 160 mg daily (42 ng/ml of propranolol in breast milk) and assuming that the infant's total ingestion will not exceed 500 ml/day, the maximum cumulative propranolol intake would be 21 μg in 24 hr. After 240 mg daily for 30 days (64 ng/ml propranolol in milk), the maximum cumulative propranolol intake would be 32 μg in 24 hr.

There appears to be no basis for the statement by Ananth (1978) that 'under no circumstances should this drug be administered to a nursing mother, and no mother taking this medication should be permitted to breast-feed her infant'.

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