Transfer of propafenone and 5-OH-propafenone to foetal plasma and maternal milk

Propafenone is a new type 1c antiarrhythmic agent (Funck-Brentano *et al.*, 1990). Since information on its use in pregnancy is sparse we report our recent experience with a 37 year old woman treated with propafenone during the last trimester of pregnancy.

At the 24th–25th week of pregnancy the occurrence of palpitations and episodes of faintness necessitated a cardiological examination. Holter monitoring revealed recurrent episodes of paroxysmal supraventricular tachycardia with non-sustained ventricular tachycardia (4b Lown class), and echocardiography was consistent with the diagnosis of right ventricular dysplasia. Propafenone was started at 150 mg four times daily orally for 3 days and then increased to 300 mg three times daily. At the latter dose Holter monitoring showed the virtual abolition of clinically significant arrhythmias. Propafenone treatment was maintained at this dose throughout the pregnancy, without any relevant adverse reaction. The increase in body weight of the patient at the end of pregnancy was 12 kg.

Delivery occurred spontaneously at the 36th week, without onset of cardiac arrhythmias. The neonatal heart rate was in the normal range both during labour and after birth (body weight: 3340 g; Apgar index: 9/10 at 1 min, 10/10 at 5 min).

Trough concentrations of propafenone and its active metabolite, 5-OH-propafenone in maternal plasma were measured by h.p.l.c. (Brode *et al.*, 1984) 1 week before delivery, at delivery and at 3 days, 4 months and 5 months after delivery. All samples, except that taken at delivery, were drawn before the morning administration of the drug (at 07.00 h). Drug and metabolite concentrations were also measured in umbilical cord plasma and in maternal milk (3 days after delivery). Milk was collected with a breast pump before drug administration and at the same time as blood sampling.

Drug binding to plasma proteins was measured by equilibrium dialysis. Plasma pH was adjusted to 7.4 with 0.3 M H_3PO_4 and dialysed against a 0.13 M phosphate buffer (pH 7.4) for 4 h at 37° C (Dianorm apparatus, 5000 m.wt. cut-off Diachema® membranes). Maternal and neonatal plasma proteins (albumin and α_1-acid glycoprotein) were also measured by immunonephelometry. The data are shown in Table 1.

Both propafenone and 5-OH-propafenone were detectable in the newborn plasma and in the maternal milk, though at concentrations lower than those found in the maternal plasma. Cord to maternal and milk to maternal plasma concentration ratios were greater for the metabolite (0.42–0.50) than for the parent drug (0.14–0.20) reflecting a difference in binding of the two compounds to maternal plasma (75% *vs* 95%, approximately). Cord plasma exhibited a lower binding capacity for both compounds compared with maternal plasma, reflecting a relatively low concentration of α_1-acid glycoprotein (albumin concentration was similar to that of the mother). It is known that propafenone has a high affinity for α_1-acid glycoprotein (Gillis *et al.*, 1985). When free concentrations of metabolite and parent drug are considered it appears that free propafenone has virtually the same concentration in maternal as in cord plasma (8 ng ml^{-1} *vs* 9 ng ml^{-1}), while free 5-OH-propafenone concentration is somewhat higher in cord plasma (17 ng ml^{-1} *vs* 25 ng ml^{-1}). This suggests that unbound drug and, to a lesser extent, unbound metabolite freely cross the placenta.

Table 1 Changes in plasma concentrations and protein binding of propafenone and 5-OH-propafenone at various times during pregnancy and after delivery

	Dose regimen						
	300 mg three times daily						*150 mg four times daily*
	1 week before delivery	*At delivery*		*3 days after delivery*		*4 months after delivery*	*5 months after delivery*
	Mother	*Mother*	*Neonate*	*Mother*	*Milk*	*Mother*	*Mother*
Concentration (ng ml^{-1})							
PROP	95	145	30	219	32	938	1052
5OHP	80	69	29	86	47	86	98
Plasma binding (%)							
PROP	89	94	71	96	—	97	97
5OHP	65	76	13	76	—	75	76
Protein concentration (g l^{-1})							
AAG	0.39	0.56	< 0.19	0.82	—	0.94	1.26
ALB	37.0	39.3	40.6	52.0	—	50.4	50.4

PROP: propafenone; 5OHP: 5-OH-propafenone; AAG: α_1-acid glycoprotein; ALB: albumin.

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Our findings on transplacental distribution are consistent with those of Brunozzi *et al.* (1988) showing that both propafenone and 5-OH-propafenone are transferred to the foetus without harmful effects during the last trimester of pregnancy.

No direct conclusions can be made regarding the possible risks of breast feeding, since the baby was fed artificially. However, based on the drug and metabolite concentrations measured in the milk and a hypothetical daily milk intake of 150 ml kg^{-1}, the amounts of drug and its active metabolite ingested would not have exceeded 16 μg and 24 μg day^{-1}, respectively. These represent a markedly subtherapeutic dose even when corrected for body weight (about 0.03% relative to the mother's dose).

Maternal plasma albumin and α_1-acid glycoprotein concentrations increased progressively after pregnancy in parallel with an augmented plasma binding capacity for both propafenone and 5-OH-propafenone.

A further observation worth noting is that trough plasma concentrations of propafenone in maternal plasma rose from 95 ng ml^{-1} at the end of pregnancy up to 938 ng ml^{-1} at the fourth month after delivery and remained substantially unchanged 1 month later (1052 ng ml^{-1}), despite the reduction of the daily dose from 300 mg three times daily to 150 mg four times daily. In the same period the free concentration of propafenone, which should be more closely related to drug effect, rose from 10 ng ml^{-1} to 28 ng ml^{-1}. In contrast, trough concentrations of 5-OH-propafenone remained relatively stable at 80–98 ng ml^{-1}.

A marked increase in plasma AUC after pregnancy has been reported for metoprolol (Hogstedt *et al.*, 1985), a drug which shares the same polymorphic metabolic pathway as propafenone (Wagner *et al.*, 1987) and to a lesser extent for other drugs that are oxidized (Dam *et al.*, 1979). Thus the metabolism of propafenone also appears to increase during pregnancy.

Further studies are required to establish the clinical significance of this observation.

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