Eur J Clin Pharmacol (1984) 27: 583–587

European Journal of Clinical Pharmacology

Pharmacokinetics of Propranolol During Pregnancy

M. F. O'Hare*, C. D. Kinney, G. A. Murnaghan, and D. G. McDevitt**

Departments of Midwifery and Gynaecology, Therapeutics and Pharmacology, The Queen's University of Belfast
Royal Maternity Hospital, Belfast, Northern Ireland

Summary. Propranolol, a beta-adrenoceptor blocking drug, was administered to 6 healthy pregnant volunteers between 32 and 36 weeks gestation and when at least 6 weeks postparum. On both occasions, subjects were given propranolol 120 mg orally or 10 mg intravenously in randomised order with a minimum washout period of 1 week. Propranolol was assayed in plasma by gas-liquid chromatography with electron-capture detection and the pharmacokinetic parameters were investigated. There were no significant alterations in elimination half-life, clearance or apparent volume of distribution per kilogram antenatally compared with postnatally: bioavailability was also unchanged. It is concluded that the disposition of propranolol is not altered during pregnancy.

Key words: propranolol, pregnancy; beta-adrenoceptor antagonist, pharmacokinetics

Beta-adrenoceptor antagonists are now established as firstline therapy for the management of hypertension. An inevitable consequence of this has been the use of these drugs in hypertension occurring in pregnancy (Lewis et al. 1977). This practice has been controversial, particularly since beta-adrenoceptor blocking drugs are known to cross the placenta (Joelsson and Barton 1969; Van Petten and Willes 1970) and several retrospective reports have suggested possible adverse effects on the fetus and neonate (Reed et al. 1974; Fiddler 1974; Lieberman et al. 1978; Pruyn et al. 1979). Recently however, controlled trials of beta-adrenoceptor antagonists in hypertension complicating pregnancy have demonstrated that atenolol was a more effective treatment than placebo (Rubin et al. 1983) and that oxprenolol was as effective as methyldopa (Fidler et al. 1983): neither drug appeared to adversely affect mother or baby.

Thus, it would appear that beta-adrenoceptor antagonists may be more widely used in pregnancy, making information about the effects of pregnancy on their disposition more important. We have recently described how pregnancy results in accelerated clearance of the relatively water-soluble, renally excreted antagonist sotalol (O'Hare et al. 1983). We now report the results of a study comparing the pharmacokinetics of propranolol, which is lipid soluble and metabolised by the liver, in human pregnancy with those obtained in the non-pregnant state.

Methods

With approval from the local University Ethical Committee and following full explanation of the purpose of the study and the procedures involved, single doses of propranolol (Inderal, ICI) were administered by the oral and intravenous route on separate occasions to 6 healthy pregnant volunteers between 32 and 36 weeks gestation. A minimum washout period of 1 week was observed between studies and the order was randomised. All patients had normal renal function as assessed by normal urea and electrolytes, the absence of proteinuria and no relevant past history. In addition, no subject had a past history of hepatic disorder. All patients were booked for delivery at Royal Maternity Hospital,

* Present address: Department of Obstetrics and Gynaecology, Daisy Hill Hospital, Newry, Co Down, Northern Ireland
** Present address: Department of Pharmacology and Clinical Pharmacology, Ninewells Hospital and Medical School, Dundee, Scotland

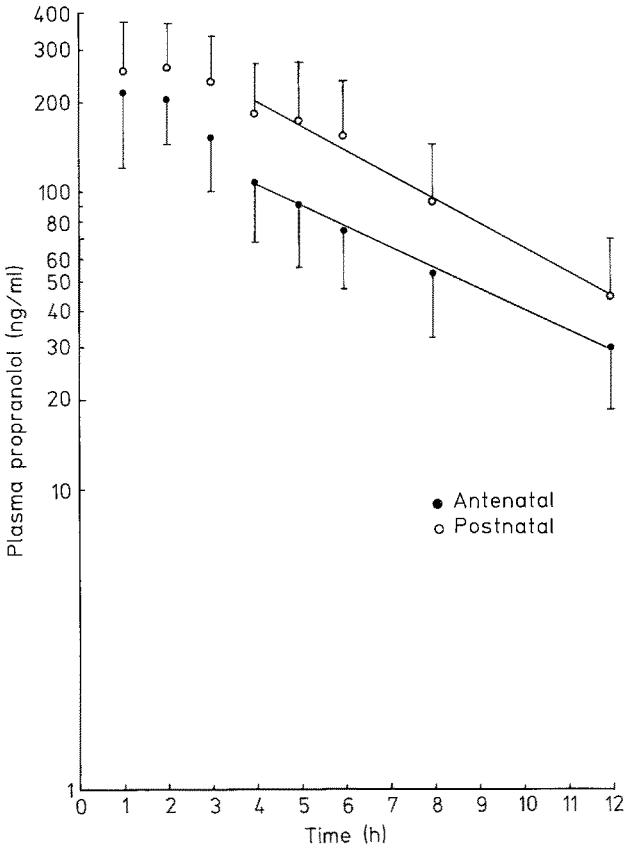

Fig. 1. Mean plasma propranolol concentration-time curves following oral administration of 120 mg antenatally and postnatally in 6 subjects

Belfast, and were subsequently delivered at or near term of healthy appropriately grown infants. Both oral and intravenous studies were repeated at least 6 weeks postpartum, after lactation had ceased and in the absence of any hormonal contraception. The details of each study were as follows:

Oral. Following an overnight fast, propranolol 120 mg was administered at 09.00 h. Six ml samples of heparinised blood were obtained at 0, 1, 2, 3, 4, 5, 6, 8 and 12 h through an indwelling venous cannula in the forearm.

Intravenous. Through an indwelling venous cannula in an upper limb, propranolol 10 mg in 10 ml was infused over 10 minutes. Six ml samples of heparinised blood were obtained through an indwelling venous cannula in the other upper limb prior to infusion, at the end of the infusion, and thereafter at 15 min, 30 min, 1, 2, 3, 4, 5, 6 and 8 h.

All heparinised blood specimens were centrifuged immediately on collection and plasma was stored at −20 °C until assay.

Propranolol Assay

Propranolol was measured in plasma by gas-liquid chromatography with electron-capture detection, using a method similar to that described for metoprolol by Kinney (1981) and using metoprolol as internal standard. The limit of sensitivity of the assay was 1 ng/ml, and investigation of the reproducibility of the method showed a coefficient of variation of 8.2% at a concentration of 40 ng/ml.

Pharmacokinetic Methods

The elimination rate constant (λ) was calculated from the terminal part of the plasma concentration/time curve by least squares regression analysis. The elimination half-life ($t_{½}$) was calculated from the equation

$$t_{½} = \frac{0.693}{\lambda}$$

The area under the plasma concentration/time curve extrapolated to infinity ($AUC_{0\rightarrow\infty}$) was obtained by the trapezoidal rule. Systemic clearance (CL) was expressed in relation to body weight and was calculated from the equation

$$CL = \frac{\text{Dose per kg body weight}}{AUC_{0\rightarrow\infty}}$$

The apparent volume of distribution (V) was calculated from the equation

$$V = \frac{CL}{\lambda}$$

Bioavailability was $AUC_{oral}/AUC_{i.v.}$ expressed as a percentage, with appropriate adjustment to allow for differences in dose between oral and intravenous routes of administration.

Statistical Methods

The results are presented as the mean ± the standard error of the mean (SEM). Statistical analyses were performed using Student's paired t-test and Wilcoxon's matched pairs signed rank test.

Results

The mean body wight of the 6 volunteers changed from 66.9 ± 3.4 kg during the antenatal studies to 58.7 ± 3.3 kg during the postnatal studies; this difference was statistically significant ($p < 0.001$) and therefore, the pharmacokinetic parameters of clearance and apparent volume of distribution were adjusted to take account of body weight before comparison.

Table 1. Mean pharmacokinetic parameters (±SEM) for propranolol in 6 subjects following oral administration and in 5 subjects following intravenous administration

	Antenatal	Postnatal
Oral (120 mg)		
$\lambda(h^{-1})$	−0.211 ± 0.048	−0.186 ± 0.008
$t_{½}$ (h)	3.9 ± 0.5	3.8 ± 0.2
$AUC_{0\to\infty}$ (μg/ml·h)	1.29 ± 0.463	1.92 ± 0.942
Bioavailability (%)	71.7 ± 30.8	69.0 ± 42.9
Intravenous (10 mg)		
$\lambda(h^{-1})$	−0.415 ± 0.084	−0.255 ± 0.032
$t_{½}$ (h)	2.1 ± 0.6	3.0 ± 0.5
$AUC_{0\to\infty}$ (μg/ml·h)	0.283 ± 0.080	0.279 ± 0.033
V (l/kg)	1.9 ± 0.5	2.7 ± 0.5
Cl (ml/min/kg)	11.3 ± 2.6	10.6 ± 1.3

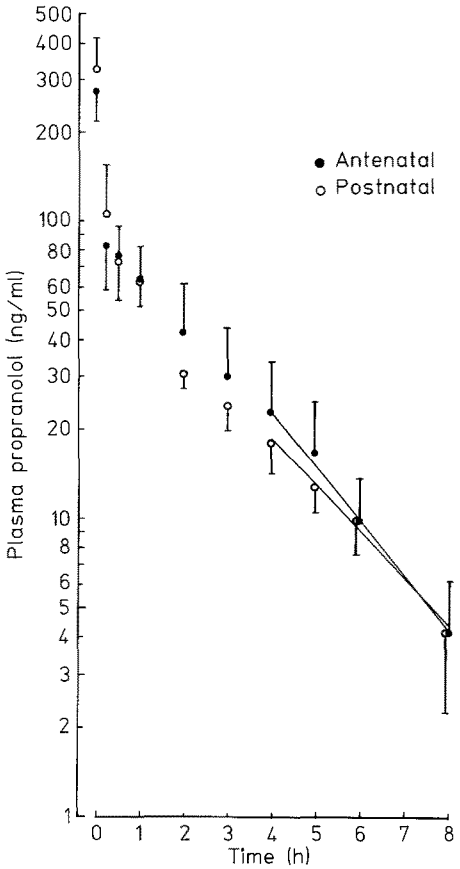

Fig. 2. Mean plasma propranolol concentration-time curves following intravenous administration of 10 mg antenatally and postnatally in 5 subjects.

Oral Administration

The mean plasma concentrations of propranolol following administration of 120 mg orally for both antenatal and postnatal phases are shown in Fig. 1, and the derived pharmacokinetic parameters are in Table 1.

The mean plasma concentrations of propranolol were consistently lower antenatally than postnatally, but the differences were not significant at any time up to 12 h. The mean time from administration to observed peak concentration in the antenatal study (1.5 h) did not differ significantly from that in the postnatal study (1.7 h; $p > 0.5$). The observed peak plasma concentration was lower antenatally than postnatally in 3 subjects and higher antenatally than postnatally in 3 subjects; in addition, there was a 28-fold variation antenatally and 13-fold variation postnatally in observed peak concentration. The elimination half-life, assessed from 4 h onwards on the individual concentration versus time curves was 3.9 ± 0.5 h antenatally and 3.8 ± 0.2 h postnatally; the difference was not significant ($p > 0.5$). There was wide intersubject variation in area under the curve ($AUC_{0\to\infty}$) reflecting the wide variation in plasma concentrations, but the difference antenatal versus postnatal was not significant ($0.5 > p > 0.1$).

Intravenous Administration

The mean plasma concentrations of propranolol following infusion of 10 mg intravenously in 5 of the 6 patients are presented in Fig. 2 and the derived pharmacokinetic parameters are in Table 1. In one patient the assay for propranolol in the antenatal study proved unsatisfactory for technical reasons, and this patient is therefore not included in this section.

Propranolol disappeared from plasma following a biexponential pattern in keeping with a two-compartment model and first-order kinetics. During the elimination phase, the mean propranolol concentration was lower postnatally than antenatally except at 6 h, but the differences were not significant. Area under the curve was similar in both studies ($p > 0.5$). The mean antenatal systemic clearance (11.3 ± 2.6 ml/min/kg) was similar to the postnatal clearance (10.6 ± 1.3 ml/min/kg; $p > 0.5$) and apparent volumes of distribution (1.9 ± 0.5 l/kg antenatally; 2.7 ± 0.5 l/kg postnatally) did not differ significantly ($p > 0.5$). Elimination half-live was assessed from 4 h onwards in 6 of the 10 log plasma concentration time curves and for shorter time periods in the remainder. The mean half-life in the antenatal study (2.1 ± 0.6 h) was shorter than in the postnatal study (3.0 ± 0.5 h) but the difference was not significant ($0.5 > p > 0.1$). Comparison of elimination half-lives intravenously and orally during and after pregnancy in the 5 subjects showed a significantly shorter half-life following intravenous than following oral administration antenatally ($p < 0.01$), but not postnatally ($0.5 > p > 0.1$).

Bioavailability

The mean bioavailability was 71.7 ± 30.8% antenatally and 69.0 ± 42.9% postnatally. These differences were not statistically significant.

Discussion

The results of this study indicate that the disposition of propranolol is not significantly altered by pregnancy, as there were no apparent differences in half-life, area under the curve, clearance and apparent volume of distribution between antenatal and postnatal studies.

The systemic clearance of 11.3 ± 2.6 ml/min/kg antenatally and 10.6 ± 1.3 ml/min/kg postnatally is comparable with 14.0 ml/min/kg previously reported in normal subjects by Evans et al. (1973). Propranolol has a high hepatic extraction ratio of about 90 per cent (Shand et al. 1971) and as a result the hepatic clearance is largely dependent on liver blood flow (Evans et al. 1973). Failure to demonstrate a change in clearance between the pregnant and non-pregnant state may simply reflect the absence of any significant alteration in hepatic blood flow in pregnancy. One might anticipate an increase secondary to the physiological rise in cardiac output and an increase from 800 ml/min to about 1400 ml/min has been reported by Tindall (1975) using a method based on bromsulphthalein excretion. However, the only study to date using direct measurement by the Fick principle failed to demonstrate any increase in liver blood flow in pregnancy (Munnell and Taylor 1947).

The apparent volumes of distribution of 1.9 ± 0.5 l/kg antenatally and 2.7 ± 0.5 l/kg postnatally, corresponding to 135–190 l/70 kg body weight, are comparable with 150 l and 216 l reported by Shand et al. (1970) and Evans et al. (1973) respectively. These volumes are greater than total body volume and indicate that propranolol is concentrated in the tissues.

The half-life of propranolol following oral administration of 3.9 ± 0.5 h antenatally and 3.8 ± 0.2 h postnatally is at the upper end of the previously reported range 2.0–3.8 h (Shand 1976) but almost identical to the half-lives obtained recently in 13 pregnant women in the third trimester (4.0 ± 0.5 h) and 3 months postpartum (4.5 ± 0.6 h) (Smith et al. 1983 b). Following intravenous administration, the values for half-life of 2.1 ± 0.6 h antenatally and 3.0 ± 0.5 h postnatally are also within the previously reported range of 1.5–3.0 h (Shand 1976). A significantly shorter half-life after intravenous than after oral administration antenatally confirms the previous report of Shand et al. (1970) in non-pregnant subjects; such a trend was evident postnatally but was not significant because it was reversed in one subject.

The bioavailability of propranolol is known to be low and highly variable, with differences as much as 20-fold in clinical practice (Shand 1976). One patient in this investigation produced unusually high concentrations in plasma following orally administered drug in both antenatal and postnatal studies, with a resulting extremely high calculation of bioavailability. Assays were performed on separate occasions and were repeated for confirmation. This cannot be readily explained, but if this patient is excluded the bioavailability range of 7–77% antenatally and 9–47% postnatally is comparable to the 16–60% range reported by Shand et al. (1970).

Thus, it would appear that pregnancy does not result in major alterations in the maternal disposition of propranolol. Similar results after oral administration only have recently been reported by Smith et al. (1983 b), although these authors did report changes in the half-life and area under the plasma concentration – time curve for naphthoxylactic acid in the third trimester of pregnancy, but not for the other major metabolites of propranolol. They suggested that N-dealkylation of propranolol and further oxidation was competitively inhibited, perhaps by endogenous steroids. On another occasion they have also produced evidence for metabolism of propranolol by the feto-placental unit (Smith et al. 1983 a). None of these changes appear likely to alter the dose requirements or apparent efficacy of propranolol during the management of hypertension in pregnancy. In this respect propranolol seems different to sotalol, which is cleared from the body more rapidly during pregnancy (O'Hare et al. 1983). The explanation may lie in the different routes of clearance for the two drugs – hepatic for propranolol and renal for sotalol.

References

Evans GH, Nies AS, Shand DG (1973) The disposition of propranolol. III. Decreased half-life and volume of distribution as a result of plasma binding in man, monkey, dog and rat. J Pharmacol Exp Ther 186: 114–122

Fiddler GI (1974) Propranolol and pregnancy (Letter). Lancet 2: 722–723

Fidler J, Smith V, Fayers P, De Swiet M (1983) Randomised controlled comparative study of methyldopa and oxprenolol in treatment of hypertension in pregnancy. Br Med J 286: 1927–1930

Joelsson I, Barton MD (1969) The effect of blockade of the beta receptors of the sympathetic nervous system of the fetus. Acta Obstet Gynecol Scand 48 [Suppl 3]: 75–79

Kinney CD (1981) Determination of metoprolol in plasma and urine by gas-liquid chromatography with electron-capture detection. J Chromatogr 225: 213–218

Lewis PJ, De Swiet M, Chamberlain GVP, Bulpitt CJ (1977) The management of hypertension in the pregnant woman. In: Lewis PJ (ed) Therapeutic problems in pregnancy. Lancaster, MTP Press Ltd, p 53–62

Lieberman BA, Stirrat, GM, Cohen SL, Beard RW, Pinker GD (1978) The possible adverse effect of propranolol on the fetus in pregnancies complicated by severe hypertension. Br J Obstet Gynaecol 85: 678–683

Munnell EW, Taylor HC (1947) Liver blood flow in pregnancy – hepatic vein catheterisation. J Clin Invest 26: 952–956

O'Hare MF, Leahey W, Murnaghan GA, McDevitt DG (1983) Pharmacokinetics of sotalol during pregnancy. Eur J Clin Pharmacol 24: 521–524

Pruyn SC, Phelan JP, Buchanan GC (1979) Long-term propranolol therapy in pregnancy; maternal and fetal outcome. Am J Obstet Gynecol 135: 485–489

Reed RL, Cheney CB, Fearon RE, Hook R, Hehre FW (1974) Propranolol therapy throughout pregnancy: a case report. Anaesth Analg 53: 214–218

Rubin PC, Butters L, Clark DM, Reynolds B, Sumner DJ, Steedman D, Low RA, Reid JL (1983) Placebo-controlled trial of atenolol in treatment of pregnancy-associated hypertension. Lancet 1: 431–434

Shand DG (1976) Pharmacokinetics of propranolol: a review: Postgrad Med J 52 [Suppl 4] 22–25

Shand DG, Nuckolls EM, Oates JA (1970) Plasma propranolol levels in adults with observations in four children. Clin Pharmacol Ther 11: 112–120

Shand DG, Evans GH, Nies AS (1971) The almost complete hepatic extraction of propranolol during intravenous administration in the dog. Life Sci 10: 1417–1421

Smith MT, Livingstone I, Eadie MJ, Hooper WD, Triggs EJ (1983a) Metabolism of propranolol in the human maternal-placental-foetal unit. Europ J Clin Pharmacol 24: 727–732

Smith MT, Livingstone I, Eadie MJ, Hooper WD, Triggs EJ (1983b) Chronic propranolol administration during pregnancy. Maternal pharmacokinetics. Europ J Clin Pharmacol 25: 481–490

Tindall VR (1975) The liver in pregnancy. Clin Obstet Gynaecol 2: 441–462

Van Petten GR, Willes RF (1970) β-Adrenoceptive responses in the unanaesthetised ovine fetus. Br J Pharmacol 38: 572–582

Received: June 7, 1984
accepted in revised form: September 17, 1984

Prof. Dr. D. G. McDevitt
Department of Pharmacology and Clinical Pharmacology
Ninewells Hospital and Medical School
Dundee, DD1 9S4, Scotland