The pharmacokinetics of oral indoramin during pregnancy

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1 The pharmacokinetics of indoramin (Baratol; Wyeth) and its active metabolite 6-hydroxyindoramin administered to 13 women as a single 37.5 mg dose of indoramin were compared under pregnant and post-partum conditions.

2 No significant differences were observed between values determined under pregnant and post-partum conditions, for any pharmacokinetic parameter. $C_{\max}$ and AUC values in individual subjects differed, in most cases, by no more than two-fold, i.e. the same order of magnitude as intra-subject variation seen in volunteers dosed repeatedly with indoramin.

3 Median values of $C_{\max}$, AUC(0,24) and $t_{1/2}$ were of a similar order to values seen previously in normal volunteers after a single 37.5 mg dose.

4 It is concluded that in treating hypertension associated with pregnancy, this study does not provide evidence to depart from the usual clinical practice of titrating indoramin dosage with control of blood pressure as the end-point, keeping in mind the restriction of the dose-limiting side-effect of sedation.

Keywords pharmacokinetics indoramin 6-hydroxyindoramin pregnancy

Introduction

Hypertension in pregnancy can often be controlled with a single agent such as methyldopa (Redman *et al.*, 1976) or a β -adrenoceptor antagonist (Thorley *et al.*, 1981; Rubin, 1981; Rubin *et al.*, 1983a).

If required, additional treatment usually takes the form of a vasodilator such as hydralazine or prazosin (Cotton *et al.*, 1985; Redman, 1980; Lubbe & Hodge, 1981; Rubin *et al.*, 1983b). During pregnancy, several physiological changes could influence drug disposition. These include increased body water, possible enhancement of liver metabolism, reduced concentration of some proteins such as albumin and increased concentration of others such as α_1 -acid glycoprotein, reduced gut motility and a large increase in renal plasma flow (Krauer *et al.*, 1980).

Indoramin (Baratol, Wyeth) is an antihypertensive agent that is used in the management of essential hypertension. It is a competitive post-synaptic α -adrenoceptor antagonist with a myocardial membrane-stabilizing component of action. Reflex tachycardia and postural hypotension are reported to be absent (Coltart, 1981), and indoramin would therefore have an advantage over older α -adrenoceptor blockers.

The aim of this study was to investigate the pharmacokinetics of indoramin after 30 weeks gestation.

Methods

Thirteen women aged 19–35 years (mean $\pm$ s.d., 25 ± 5 years) attending the maternity section of

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the Tygerberg Hospital were studied from January to December 1985. The study was approved by the Ethics Committee of the University of Stellenbosch and informed consent was obtained from all subjects. Their body mass ranged from 51.6–76.6 kg (mean $\pm$ s.d., 62.8 ± 9.6 kg) and their gestation on beginning indoramin was 31–38 weeks (mean $\pm$ s.d., 34.5 ± 1.8 weeks). Only patients who were pregnant at or beyond 30 weeks gestation and diagnosed as hypertensive after at least 20 weeks of their pregnancies were included in this study. For the purposes of this study, hypertension was defined as a diastolic blood pressure greater than 90 mm Hg on two occasions 24 h apart or greater than 99 mm Hg on two occasions 8 h apart as measured with a Reister semi automated sphygmomanometer in the sitting, left lateral lying and standing positions after 3 min rest. Patients were free of other complicating disease and hence were not receiving other therapy. No attempt was made to differentiate between pre-eclampsia and hypertension.

On admission to the study, all patients were placed in a special care unit and received a single dose (37.5 mg) of indoramin, after which blood for indoramin analysis was drawn at 0, 1, 2, 3, 4, 5, 6, 8, 12 and 24 h. The following day the indoramin dose was increased to 25 mg 12 hourly and after that the dose was increased until control of blood pressure was satisfactory, with a maximum daily dose of 150 mg. Control of blood pressure was defined as a diastolic blood pressure of less than 90 mm Hg in the sitting position. The patients were maintained on the dose that controlled blood pressure until delivery, when treatment was terminated. Maternal and foetal progress were assessed by means of daily blood pressure, maternal and foetal heart rates and cardiotocography. Serial ultrasonic biparietal diameter measurements were made fortnightly.

At delivery, the time of the last dose of indoramin was noted and maternal and umbilical blood samples were taken for indoramin assay. Indoramin administration was stopped at this point. Neonates were given a full paediatric assessment, including Apgar score and neonatal blood sugar, and plasma indoramin concentrations were measured 3 h after delivery.

In the puerperium a further series of blood samples were taken for indoramin assay at 0, 1, 2, 3, 4, 5, 6, 8, 12 and 24 h following a single dose of 37.5 mg indoramin on day 10 after delivery.

Plasma concentrations of indoramin and 6-hydroxyindoramin were measured by high performance liquid chromatography with fluorimetric detection according to the method

described in GT/MR 12142 (unpublished results. Study no GT/MR 12142, Wyeth, London, 1986). This method has a coefficient of variation of 3.5–5.3% over the range of observed indoramin concentrations, and 5.5–13.7% over the range of observed 6-hydroxyindoramin concentrations. Pharmacokinetic parameters calculated after oral dosing included time of maximum plasma drug concentration ($t_{\max}$); observed maximum plasma concentration ($C_{\max}$) and area under the curve of plasma drug concentration vs time up to 8 (AUC(0,8 h)) or 24 h (AUC(0,24 h)) calculated by the trapezoidal method.

The terminal phase disposition half-life ($t_{1/2,z}$) was determined from the slope of the best-fit line after linear regression through the terminal phase of the curve of log (plasma drug concentration) vs time. For 6-hydroxyindoramin, $t_{\max}$, $C_{\max}$ and AUC(0,8 h) were determined. The terminal disposition half-life ($t_{1/2,z}$) could not be determined for the metabolite because its limit of measurement (5 ng ml⁻¹) did not permit accurate definition of the terminal phase.

Statistical analysis was done using the paired *t*-test (two-tailed) and the Wilcoxon matched pairs signed rank test.

Results

The absorption of indoramin in pregnant women was quite rapid, peak plasma drug concentrations being observed at approximately 3.5 h after dosing (Table 1). Drug concentrations in plasma varied quite widely between patients, with $C_{\max}$ values ranging from 3.9 to 52.4 ng ml⁻¹ (median 10.4 ng ml⁻¹). Elimination occurred quickly with a median $t_{1/2,z}$ value of 4.1 h (Figure 1, Table 3). Maximum concentrations of the metabolite 6-hydroxyindoramin (median 7.8 ng ml⁻¹) were achieved at around the same time as those of unchanged drug, i.e. about 3 h after dosing (Figure 1, Table 4).

In the day 10 post-partum phase of the study, drug absorption was also rapid. The median $t_{\max}$ value of 2.0 h was slightly shorter post-partum than during pregnancy, though the difference failed to reach statistical significance (Tables 2 and 3). The median $C_{\max}$ value, 15.3 ng ml⁻¹ (range 2.9–87.9 ng ml⁻¹), was similar to that observed in the pregnant women, and elimination also occurred at a similar rate, with a median half-life of 3.5 h. Consequently the overall bioavailability was similar under the two conditions, as is indicated by median areas under the plasma drug concentration vs time curve (AUC(0,24 h)) of 73.2 ng ml⁻¹ h in the post-partum phase of the study compared with

Table 1 Plasma concentrations of indoramin in 13 pregnant and post-partum women following a single 37.5 mg oral dose

Time after dosing (h)	Plasma concentration (ng ml ⁻¹)							
	Pregnant				Post-partum			
	mean	s.e. mean	median	range	mean	s.e. mean	median	range
Pre-dose	<2		<2		<2		<2	
1	7.5	2.7	3.0	<2–26.0	9.3	4.6	<2	<2–43.4
2	7.5	2.3	5.9	<2–27.0	14.2	3.4	13.2	2.9–42.7
3	12.1	3.0	8.1	2.9–35.6	12.6	3.8	9.8	<2–51.3
4	10.4	1.9	8.5	3.9–25.2	15.0	6.8	7.6	<2–87.9
5	8.0	1.3	7.7	2.5–17.2	8.4	2.7	4.8	<2–35.2
6	7.4	2.1	5.5	2.7–27.4	8.0	3.0	5.2	<2–39.3
8	8.6	4.0	5.2	<2–52.4	7.6	4.0	3.6	<2–51.1
12	4.5	3.1	2.0	<2–35.3	7.4	5.3	2.2	<2–65.9
24	3.3	2.6	<2	<2–30.6	3.4	3.2	<2	<2–38.3

Table 2 Plasma concentrations of 6-hydroxyindoramin in 13 pregnant and post-partum women given a single 37.5 mg oral dose of indoramin

Time after dosing (h)	Plasma concentration (ng ml ⁻¹)							
	Pregnant				Post-partum			
	mean	s.e. mean	median	range	mean	s.e. mean	median	range
Pre-dose	<5	—	<5		<5	—	<5	
1	<5	—	<5	<5–32.6	5.6	2.6	<5	<5–26.7
2	<5	—	<5	<5–24.5	9.7	2.1	11.6	<5–18.7
3	6.4	2.2	<5	<5–20.5	6.1	1.7	5.5	<5–17.2
4	4.9	2.1	<5	<5–19.5	4.3	2.0	<5	<5–18.1
5	<5	—	<5	<5–16.2	<5	—	<5	<5–11.0
6	<5	—	<5	<5–6.9	<5	—	<5	<5–9.8
8	<5	—	<5	<5–10.4	<5	—	<5	<5–9.2
12	<5	—	<5	<5–6.5	<5	—	<5	<5–6.5
24	<5	—	<5	<5–10.2	<5	—	<5	<5

Table 3 Pharmacokinetic parameters derived from plasma concentrations of indoramin following a single 37.5 mg oral dose to 13 pregnant and post-partum women

Parameter	Plasma concentration (ng ml ⁻¹)							
	Pregnant				Post-partum			
	mean	s.e. mean	median	range	mean	s.e. mean	median	range
<i>t</i> _{max}	3.4	0.6	3.5	1.0–8.0	—	—	2.0	1.0–4.0
<i>C</i> _{max}	16.3	4.0	10.4	3.9–52.4	21.7	6.7	15.3	2.9–87.9
<i>t</i> _{1/2,z}	4.0	0.3	4.1	2.3–5.6	3.8	0.4	3.5	2.4–5.8
AUC (0,8 h) (ng ml ⁻¹ h)	66.3	15.0	47.0	16.8–197	80.2	27.7	55.4	3.9–366
AUC (0,24 h) (ng ml ⁻¹ h)	138.6	58.6	81.2	16.8–767	173.7	96.7	73.2	3.9–1225

Figure 1 Plasma concentrations of indoramin in pregnant (○) and post-partum (■) women following a single 37.5 mg oral dose.

Table 4 Pharmacokinetic parameters derived from plasma concentrations of 6-hydroxyindoramin following a single 37.5 mg oral dose of indoramin to 13 pregnant and post-partum women

Parameter	Plasma concentration (ng ml ⁻¹)							
	Pregnant				Post-partum			
	mean	s.e. mean	median	range	mean	s.e. mean	median	range
$t_{\max}$	—	—	3.0	1.0–4.0	—	—	2.0	1.0–4.0
$C_{\max}$ (ng ml ⁻¹ h)	10.2	2.8	7.8	<5–32.6	13.2	1.9	13.2	<5–26.7
AUC (0,8 h) (ng ml ⁻¹ h)	28.6	11.9	<37.5	5.6–140	30.7	6.6	<37.5	8.8–88.9

81.2 ng ml⁻¹ h during pregnancy. Plasma concentrations of 6-hydroxyindoramin on day 10 post-partum (e.g. median $C_{\max}$ 13.2 ng ml⁻¹) were not significantly different from those in the pregnant state.

Discussion

From the results of this study, it appears that pregnancy does not have any significant effect on the pharmacokinetics of a single 37.5 mg dose of indoramin. Values of $C_{\max}$, AUC(0,24 h) and $t_{1/2}$ were not significantly altered in pregnancy compared with the post-partum condition and, furthermore, were of a similar order to values seen in normal volun-

teers after a single 37.5 mg oral dose (unpublished results. Study no GT/MR 12399, Wyeth, London, 1986). Although the subjects in this latter study were male, an absence of effect of gender on indoramin kinetics has been reported (Norbury *et al.*, 1983).

The post-partum values were determined after 10 days, as re-admission of indigent patients 3 months after delivery is difficult. Furthermore, the plasma indoramin concentrations during pregnancy and 10 days post-partum did not differ significantly from those reported in the abovementioned study carried out in normal volunteers. Admittedly, 10 days post-partum is very short, but it was considered that waiting longer would not have produced a significant difference.

Inter-subject variability in plasma indoramin concentrations was extensive in the pregnant and post-partum women, but no more so than in normal volunteers. For example $C_{\max}$ and AUC values in the pregnant women varied thirteenfold and forty-sixfold, respectively. By comparison, differences between $C_{\max}$ and AUC values in the same subject in the pregnant and post-partum conditions were generally not much more than twofold, i.e. of the same order as the intra-subject variation observed in volunteers on repeated administration of the drug to the same individuals (unpublished results. Study no GT/MR 13564, Wyeth, London, 1986).

Because of the well recognized inter-subject variation in response to indoramin, the dosage of this drug is usually titrated to blood pressure control keeping in mind the restrictions imposed by the dose-limiting side-effect of sedation. The results of the present study suggest no reason to alter this practice in treating hypertension arising during pregnancy.

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