CLINICAL PHARMACOLOGICAL STUDIES WITH PRAZOSIN DURING PREGNANCY COMPLICATED BY HYPERTENSION

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- 1 The disposition and effect of orally administered prazosin have been studied in eight women with hypertension which was uncontrolled by β -adrenoceptor blockade during the last trimester of pregnancy. Results were compared with healthy men of similar age.
- 2 The median time to peak concentration was 165 min during pregnancy and 120 min in the men ($P < 0.04$). Area under the concentration vs time curve was 3914 ng l⁻¹ min in pregnancy and 2439 ng l⁻¹ min in the men ($P < 0.06$). Mean elimination half-life was 171 min in the pregnant women and 130 min in the men ($P < 0.01$).
- 3 Blood pressure was lowered by prazosin in both supine and standing positions. Blood pressure control remained satisfactory in six of the eight women and the median prolongation of pregnancy was 22 days. Neonatal outcome was satisfactory and all babies are developing normally.
- 4 We conclude that prazosin is more slowly, but apparently more completely, absorbed during pregnancy and that its half-life is slightly prolonged. Prazosin appears to be both effective and safe when used during the last trimester to control blood pressure.

Keywords prazosin pregnancy hypertension

Introduction

Many patients who have hypertension during pregnancy can be controlled on a single agent such as a β -adrenoceptor blocker (Thorley *et al.*, 1981; Rubin, 1981; Rubin *et al.*, 1983) or methyldopa (Redman *et al.*, 1976). When additional treatment is required this usually takes the form of a vasodilator such as hydralazine (Gallery *et al.*, 1979) or prazosin (Lubbe & Hodge, 1981). In common with many other drugs, little is known about the clinical pharmacological aspects of vasodilator use in pregnancy. There are several physiological changes during pregnancy which could influence drug disposition. These include reduced gut motility, reduced concentration of some proteins such as albumin and increased concentration of others such as α_1 -acid glycoprotein, increased body water, a near doubling of renal plasma flow and a probable enhancement of liver metabolism (Krauer *et al.*, 1980). It has been our practice to add prazosin when a β -adrenoceptor blocker alone proves unsuccessful in controlling hypertension during pregnancy. We have used the opportunity afforded by this policy to study some aspects of prazosin disposition and effect during the last trimester.

Methods

Eight women were studied. Their ages ranged from 18–33 years with a median of 24 and their gestation on beginning prazosin was 32–37 weeks with a median of 35 weeks. In all cases the blood pressure lying supine was above 140/90 mm Hg on several occasions over at least 24 h in spite of treatment with the β -adrenoceptor antagonist, atenolol 200 mg day for at least 3 days. In each case the obstetrician concerned wished to prolong the pregnancy. None of the women had proteinuria and no attempt has been made to differentiate between essential hypertension and pregnancy associated hypertension.

When it was decided to introduce prazosin, 1 mg of the drug was given orally at 08.30 h. Blood pressure was recorded both supine and following 2 min standing using an automated sphygmomanometer (Bosomat 11D) before drug administration, at intervals of 30 min for 3 h and hourly until 8 h had elapsed. Blood for prazosin analysis was drawn through an indwelling venous cannula at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7 and 8 h following drug administration. Foetal heart rate was recorded at regular intervals during the day.

The dose of prazosin was subsequently adjusted in

order to achieve optimum blood pressure control. The clinical course of both mother and baby was subsequently monitored.

Prazosin concentration was measured in whole blood using the high pressure liquid chromatography method previously described (Yee *et al.*, 1979). This method has a coefficient of variation of 5–10% over the range of concentrations studied. Pharmacokinetic analysis was by conventional methods for data follow-

ing oral administration of a drug (Rubin *et al.*, 1981). The values for time to peak concentration, area under the concentration vs time curve extrapolated to infinity (AUC_0^∞) and half-life were compared with those obtained in healthy young men of similar age who were studied using an identical protocol, the results of which have previously been reported (Rubin *et al.*, 1981). Comparisons were by the Wilcoxon rank sum test.

Figure 1 Prazosin concentration (mean $\pm$ s.d.) in pregnant women (●) and normal men of similar age (○) following 1 mg dose.

Figure 2 Prazosin elimination half-life in pregnant women and normal men of similar age. $P < 0.01$.

Results

The time profile of prazosin concentration in the pregnant women and male volunteers is shown in Figure 1. Prazosin was absorbed more slowly but apparently more completely in the pregnant patients. The median time to peak concentration was 165 min (range 120–420) in the pregnant women compared with 120 min (90–180) in the healthy young men ($P < 0.04$). During pregnancy the AUC_0^∞ was 3914 ng l⁻¹

min (182–7997) and 2439 ng l⁻¹ min (1440–3452) in the men ($P < 0.06$). The elimination half-life of prazosin was significantly longer in the pregnant group (Figure 2).

There was a significant ($P < 0.01$) reduction in both supine and standing blood pressure following the first dose of prazosin with the effect being apparent by 0.5 h, greatest at 3 h and largely resolved by 6 h (Figures 3 and 4). Three women felt dizzy on standing at the 3 h recording but there were no cases of syncope or any

Figure 3 Supine blood pressure (mean $\pm$ s.d.) following initial 1 mg dose of prazosin in women with hypertension during the last trimester of pregnancy.

Figure 4 Standing blood pressure (mean $\pm$ s.d.) following initial 1 mg dose of prazosin in women with hypertension during the last trimester of pregnancy.

other serious adverse effects. There were no significant changes in foetal heart rate during the study. The doses of prazosin which were subsequently used were 1 mg twice daily in five patients, 2 mg three times daily in one, 5 mg twice daily in one and 5 mg three times daily in the remaining patient. The median duration of prazosin therapy was 22 days with a range of 1–96 days. Blood pressure control was generally good, with systolic BP remaining between 110 and 140 mm Hg and diastolic BP between 60 and 90 mm Hg in all but the two patients on the highest dose. None of the patients went on to develop proteinuria.

The neonatal outcome is shown in Table 1. With the exception of one baby who developed hypoglycaemia and hypocalcaemia there were no serious neonatal problems. All babies left the hospital in good health and all are developing normally as assessed at regular follow up over 6 to 30 months.

Discussion

Prazosin proved to be an effective antihypertensive agent in women whose blood pressure had not responded to a β -adrenoceptor blocker alone. This confirms the finding of Lubbe & Hodge (1981) that prazosin is a useful agent in the more severe forms of non-proteinuric hypertension during pregnancy. As with their study we found that none of the women went on to develop proteinuria. The effect on blood pressure was sustained for a median of 22 days which is a period during which substantial foetal lung maturation can occur. In six of the eight patients prazosin was effective at low doses while the two women receiving the higher doses were not well controlled. This would suggest that if prazosin is going to lower blood pressure in pregnancy it will do so at a modest dose.

The perinatal outcome was generally satisfactory,

given that all women had high risk pregnancies. None of the babies had prolonged clinical problems and all are developing normally 6–30 months following delivery.

A complete pharmacokinetic study requires data following intravenous as well as oral administration of a drug. There have been recurring pharmaceutical problems with intravenous formulations of prazosin. At the time this study was undertaken an intravenous formulation was not available. It was therefore necessary to draw limited conclusions on the basis of the data available. We have previously shown that concurrent β -adrenoceptor blockade does not influence the disposition of prazosin (Rubin *et al.*, 1980). The observed changes suggest about a 60% greater absorption of prazosin during pregnancy, though there was considerable variability in AUC. Not surprisingly perhaps, the patient with the lowest AUC was the one receiving the highest final dose of prazosin. The bioavailability of prazosin is usually of the order of 0.68 (Rubin *et al.*, 1981) with most, but not all, of the deficit being accounted for by presystemic liver metabolism (Rubin *et al.*, 1979). If the increased AUC represents a genuine increase in bioavailability then the most likely explanation would be a reduction in presystemic liver metabolism in pregnancy.

Half-life showed an approximately 25% increase in pregnancy. Prazosin ordinarily has a relatively low volume of distribution of around 0.6 l kg^{-1} (Rubin *et al.*, 1981) and is highly protein bound with its free fraction negatively correlated to serum albumin concentration (Rubin & Blaschke, 1980). The decreased albumin concentrations of pregnancy could lead to an increased prazosin volume of distribution. An alternative possibility is that the enzymes mediating prazosin *O*-demethylation are relatively inhibited during pregnancy as has previously been suggested for pethidine demethylation (Crawford & Rudofsky, 1966). In the absence of a study with intravenous

Table 1 Clinical details of neonates born to mothers who received atenolol and prazosin

Patient	Delivery	Gestation	Weight (kg)	Placental weight (g)	Apgar 1 5 min	Problems
1	Forceps	38+	2.76	445	7,9	Jaundice
2	Emergency C S	38	2.72	400	9,9	Small for dates
3	SVD	38	3.02	670	8,9	
4	SVD	39+	2.38	400	9,10	
5	Elective C S	34	1.86	360	8,9	Jaundice
6	SVD	40	2.92	398	9,10	
7	SVD	39	2.50	395	8,10	Hypoglycaemia Hypocalcaemia
8	C S	36	3.14	650	10,10	Rash

Gestation assessed by Dubowitz method

SVD: spontaneous vaginal delivery

C S: Caesarean section

administration it is not possible to determine the relative contribution of changes in volume of distribution and clearance to the prolonged half-life of prazosin.

In conclusion, prazosin appears to have a greater bioavailability in pregnant women than in men of similar age and is possibly also eliminated more slowly. The antihypertensive efficacy of the drug at

low doses is in keeping with these possibilities. We suggest that prazosin can safely be used during pregnancy when a β -adrenoceptor blocker alone is insufficient but, as in non obstetric practice, the starting dose should be 0.5 mg and the drug is likely to be effective in doses of 2 or 3 mg/day.

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