LABETALOL DISPOSITION AND CONCENTRATION-EFFECT RELATIONSHIPS DURING PREGNANCY

PETER C. RUBIN, LUCY BUTTERS, ANDREW W. KELMAN,
CLARE FITZSIMONS & JOHN L. REID

University Department of Materia Medica, Stobhill General Hospital, Glasgow, G21 3UW

1 Labetalol pharmacokinetics and concentration-effect relationships following intravenous administration have been studied in 10 women during the last trimester of pregnancies complicated by hypertension, in seven of these women postpartum (when normotensive) and in 10 normotensive female volunteers.

2 The clearance and volume of distribution of labetalol were the same in all three groups. Clearance values ($l\ min^{-1}$) were: pregnant, 2.16 (range 1.54–3.14); postpartum 2.35 (1.56–3.85); controls 1.96 (0.98–2.61). Volumes of distribution (l) were: pregnant 274 (250–547); postpartum 407 (248–701); controls 234 (186–415).

3 A linear model relating labetalol concentration to effect successfully described the antihypertensive action of labetalol in the pregnant patients. Supine systolic blood pressure fell by 0.38 (0.14–0.91) mm Hg per $ng\ ml^{-1}$ of labetalol and diastolic by 0.36 (0.21–1.14) mm Hg per $ng\ ml^{-1}$ of labetalol. In the other two groups labetalol did not lower pressure sufficiently to allow modelling to be performed.

4 We conclude that pregnancy does not alter the clearance or volume of distribution of labetalol. Modelling techniques can be applied successfully to drug induced blood pressure changes during pregnancy.

Introduction

The emphasis on teratogenesis which followed the thalidomide tragedy has tended to overshadow the legitimate use during pregnancy of drugs in the management of conditions such as asthma, epilepsy and hypertension. Little is known about the principles which should determine the most effective use of drugs in these circumstances and yet the physiological changes during pregnancy could be expected to influence both drug disposition and effect. Gut transit time is prolonged (Parry *et al.*, 1970), serum proteins undergo substantial changes in concentration (Studd *et al.*, 1970) body water and body fat increase (Hytten & Leitch, 1971), renal plasma flow almost doubles (Dunlop, 1976) and liver metabolism probably increases (Davis *et al.*, 1973). The possibility of changes in the effect of drugs acting on the adrenergic nervous system is suggested by the observation that oestrogens increase the ratio of α_2 - to β -adrenoceptors (Hoffman *et al.*, 1981).

The adrenoceptor antagonist labetalol has been used widely in the management of hypertension occurring during pregnancy (Riley & Symonds, 1982). We describe here the results of a study which

had two main aims. First to determine whether pregnancy influences the clearance of labetalol. Second, to assess the applicability of concentration-effect modelling techniques to clinical pharmacological studies during pregnancy.

Methods

The protocol was approved by the Research and Ethical Committee of the Greater Glasgow Health Board, Northern District and all subjects gave written consent after the nature of the study had been carefully explained to them.

Subjects and experimental methods

Ten women aged 18–37 years who developed hypertension during the last trimester of pregnancy, and who were about to be commenced on labetalol for treatment of raised blood pressure, received their first dose of drug as 50 mg given intravenously over 2 min. Gestation at the time of study ranged from 33–38

weeks. Blood was drawn through an indwelling venous cannula in the opposite arm at 0, 5, 10, 15, 20, 30, 40 min, and 1, 1.5, 2, 2.5, 3, 4, 6 and 8 h. Blood samples were centrifuged and the plasma stored at -20°C until the labetalol concentration was analysed by high pressure liquid chromatography using fluorescence detection (Meredith *et al.*, 1982). In our laboratory this method has a lower limit of sensitivity of 10 ng/ml with an average coefficient of variation of 5%. Blood pressure and heart rate were determined following 20 min quiet supine rest and after 5 min standing before drug administration and again at 30 min intervals until 3 h then at hourly intervals until 8 h following labetalol. Blood pressure was measured by the same observer using a mercury sphygmomanometer. Between blood pressure recordings subjects rested in the recumbent position except when taking lunch or visiting the bathroom. None of the women was receiving any concurrent drug therapy, all were in good health except for their hypertension and all had normal biochemical and haematological indices.

Seven of these 10 women agreed to return for a repeat of this study 3–4 months postpartum. Exactly the same protocol was followed. Again, none of the women was taking oral contraceptives or any other medication and all were by this time normotensive ($<120/80$ mm Hg supine) and had been off treatment since delivery.

Ten women aged 18–35 years who were not taking an oral contraceptive or any other medication, and who had not been pregnant for at least 2 years (three) or had never been pregnant (seven) and who were in good health were also studied using the same protocol.

Pharmacokinetic analysis

Plasma concentration vs time data were fitted to a biexponential function of the form:

$$C = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

using a non linear least squares regression programme based on the Marquardt algorithm (Bevington, 1969) with reciprocal weighting on a Nodecrest V76 digital computer. The area under the concentration vs time curve (AUC) during the blood sampling period was calculated using the trapezoidal rule. The extrapolated area beyond the last data point was calculated by dividing the concentration at the time of the last sample by the terminal slope obtained from the computer fit of the data. Clearance (CL) was calculated from the model-independent expression

$$\text{CL} = \frac{\text{Dose}}{\text{AUC}}$$

The coefficients of the biexponential equation were used to calculate the volume of distribution at

steady state (V_{ss}) according to standard techniques assuming a two compartment open model with elimination from the central compartment.

Pharmacodynamic analysis

Conventional pharmacokinetic analysis is concerned with finding the mathematical model which best describes the change in drug concentration over time. Since it is drug *effect* rather than drug *concentration* which is of ultimate importance, potentially interesting and useful information could be derived from determining the model which best describes the relationship between drug concentration and effect. In the context of the present study, we were concerned to discover whether pregnancy influenced the concentration-effect profile of labetalol. Several techniques have been applied to pharmacodynamic modelling (Whiting & Kelman, 1980). The approach adopted here was first suggested by Sheiner *et al.* (1979) and involves the extension of the pharmacokinetic model to include a hypothetical effect compartment (Figure 1). The amount of drug in this compartment is considered to be negligible in relation to the total amount of drug in the body. Thus the presence of this additional theoretical compartment does not influence the parameters of the original pharmacokinetic model. The amount of drug in the effect compartment (A_e) is calculated, as described by Sheiner *et al.* (1979), by solving the equation:

$$\frac{dA_e}{dt} - k_{1e}A_1 = k_{eq}A_e \quad (2)$$

where A_1 is the amount of drug in the central compartment and k_{1e} and k_{eq} are first order rate con-

Figure 1 Pharmacokinetics model with effect compartment. k_{12} and k_{21} are the rate constants for drug transfer between central and peripheral compartments. Drug is eliminated from the central compartment with rate constant k_{10} . The amount of drug in the effect compartment and the rate constant k_{1e} are considered too small to influence the pharmacokinetic model. The rate constant k_{eq} describes the time lag between changing plasma concentration and effect. All rate constants are first order.

stants. The concentration of drug in the effect compartment, C_e , is then related to effect, E , by the relationship:

$$E = f(C_e) \quad (3)$$

where f can be linear or sigmoid. In the simplest case, where f is linear, this equation becomes:

$$E = mC_e + i \quad (4)$$

The term ' m ' represents a sensitivity factor, in this case the slope of the concentration effect line: mm Hg per ng ml^{-1} labetalol. The ' i ' factor is baseline measurement when $C_e = 0$. In view of the limited range of blood pressure response, we considered this linear model to be adequate. Parameters were obtained by nonlinear regression using an iterative procedure based on the Marquardt algorithm (Bevington, 1969).

Statistics

Results are expressed as median (and range) with comparisons made by paired or unpaired Wilcoxon tests as appropriate.

Results

Most subjects experienced mild, transient tingling of the scalp following labetalol injection but there were no other adverse effects. In all cases a good fit was obtained with the concentration vs time data and all coefficients of determination exceeded 0.9. The major kinetic indices are shown in Table 1. There was no difference between groups in clearance, V_{ss} or half-life either when results were analysed as absolute values or expressed in terms of unit weight. When data analysis was limited to the seven women studied both during and following pregnancy there was still no significant difference in clearance, and the median values were more closely approximated. Clearance ($\text{ml min}^{-1} \text{ kg}^{-1}$) expressed as median and range for

these women was 31.3 (21.9–38.8) during pregnancy and 34.8 (27.6–51.4) following pregnancy.

Labetalol produced a prompt and sustained fall in blood pressure when given to the women with hypertension during pregnancy (Figure 2). However, when

Figure 2 Average supine systolic and diastolic blood pressure following labetalol 50 mg intravenously in (a) 10 pregnant women during the last trimester, (b) seven of these women 3–4 months postpartum and (c) 10 female volunteers.

Table 1 Pharmacokinetic indices following intravenous administration of labetalol.

	Pregnant (n = 10)	Postpartum (n = 7)	Age-matched women (n = 10)
Clearance (l min^{-1})	2.16 (1.54–3.14)	2.35 (1.56–3.85)	1.96 (0.98–2.61)
V_{ss} (l)	274 (250–547)	407 (248–701)	234 (186–415)
$t_{1/2}$ (min)	147 (111–167)	152 (116–195)	126 (97–158)
Clearance ($\text{ml min}^{-1} \text{ kg}^{-1}$)	24.8 (19.7–38.8)	34.8 (27.6–51.4)	33.8 (20.4–41.6)
V_{ss} (l kg^{-1})	3.7 (2.4–6.8)	6.3 (3.3–9.3)	3.9 (3.0–6.5)

Table 2 Parameters of effect model equation: $E = mCe + i$

Subject	Supine						Standing					
	m	Systolic i	r ²	m	Diastolic i	r ²	m	Systolic i	r ²	m	Diastolic i	r ²
PS	-0.33	126	0.52	-0.46	94	0.82	-0.22	125	0.87	-0.14	89	0.82
SA	-0.34	139	0.82	-0.26	99	0.80	-0.84	167	0.84	-0.33	115	0.74
SW	-0.14	115	0.41	-1.14	89	0.61	—	—	—	-0.24	89	0.89
MM	-0.42	131	0.00	-0.21	92	0.79	—	—	—	—	—	—
JM	-0.91	123	0.69	-0.99	87	0.74	-1.13	128	0.92	-1.10	87	0.91
LK	-0.49	134	0.62	-0.78	93	0.75	-0.94	144	0.90	-0.70	104	0.85
CP	—	—	—	—	—	—	—	—	—	-0.18	98	0.72

the same women were studied 3–4 months postpartum, by which time they were normotensive, there was no clearly discernible effect on blood pressure. Similarly, the normotensive control group showed a very modest response to labetalol. The parameters of the equation relating labetalol concentration to blood pressure for the pregnancy group are shown in Table 2 and a representative graph of calculated and observed blood pressure is shown in Figure 3. Modelling was unsuccessful in the postpartum and control groups because of the very limited change in blood pressure.

Figure 3 Observed (●) and calculated (Δ) supine diastolic blood pressure in a representative subject (SA). $r^2 = 0.80$.

Discussion

In addition to the general physiological considerations detailed above, suggestions that drug disposition might be altered in pregnancy derive mainly from observations with anticonvulsants. Several groups have reported increased dosage requirements of phenytoin, phenobarbitone and carbamazepine during pregnancy with a return to normal following delivery (Mygind *et al.*, 1976; Lander *et al.*, 1977; Dam *et al.*, 1979; Landon & Kirkley, 1979; Kochenour *et al.*, 1980). The reasons for these changes are

unclear. Although the protein binding of phenytoin decreases during pregnancy, this is not the explanation for lower plasma levels since the concentration of free phenytoin falls also (Chen *et al.*, 1982). Two groups have studied the excretion of the major phenytoin metabolite, 5-(*p*-hydroxyphenyl)-phenylhydantoin (HPPH) as well as measuring plasma concentrations of parent drug (Landon & Kirkley, 1979; Kochenour *et al.*, 1980). Both groups found a decrease in plasma phenytoin concentration during pregnancy but in neither study was there any convincing change in HPPH excretion, suggesting that increased metabolism is not likely to be the explanation for the observed changes. In contrast, when the 10-11-epoxy metabolite of carbamazepine was measured in plasma simultaneously with carbamazepine, the ratio of metabolite to parent drug increased during pregnancy. This suggests an increase in metabolism to explain falling carbamazepine concentrations (Dam *et al.*, 1979). Changes in pharmacokinetics have been seen with drugs other than anticonvulsants. Methimazole has been reported to have an apparent clearance in pregnant hyperthyroid patients which is significantly greater than in non-pregnant women (Skellern *et al.*, 1980). The only report suggesting the possibility of reduced clearance in pregnancy is the finding that caffeine has a longer half life in pregnant women compared to non-pregnant controls (Knutti *et al.*, 1981). All these studies have involved oral administration of drug and it has therefore not been possible to perform a reliable calculation of clearance. We therefore carried out the investigation described here using intravenous administration of labetalol with postpartum women acting as their own controls.

There was no difference in clearance or V_{ss} between the pregnancy and postpartum studies in the seven women who were studied on each occasion. We considered one possible reason for this could have been that we had performed the postpartum study too soon following pregnancy, before all the metabolic and haemodynamic changes had resolved. Although this was unlikely, particularly since anticonvulsant requirements return to normal within a few days, we

proceeded to carry out the same study in women most of whom had never been pregnant and none of whom had been pregnant within two years. Again we found no difference from the pregnancy values for clearance and V_{ss} .

Labetalol is eliminated from the body mainly as a conjugate (Hopkins *et al.*, 1978) and its high rate of clearance, approximating reported values for human liver blood flow (Grayson & Mendel, 1965) would suggest that it will demonstrate flow dependent kinetics (George, 1979). Two inferences can, therefore, be drawn from our findings. First, although there is some evidence that the hepatic mixed function oxidases are induced during pregnancy (Davis *et al.*, 1973; Dam *et al.*, 1979) the enzyme system which mediates labetalol conjugation appears not to be influenced in this way. The mechanism of mixed function oxidase induction during pregnancy is presumed to be hormonal, with progestogens causing induction and oestrogens inhibition (Hunter, 1976). On the basis of currently available information, this hormonal action must be considered selective for specific enzyme systems. The second inference is that any changes in liver blood flow which occur during pregnancy are insufficient to alter substantially the pharmacokinetics of flow limited drugs.

The second part of this study was concerned with trying to assess whether pregnancy alters the pharmacodynamics of labetalol. One advantage of the linear form of the effect model proposed by Sheiner *et al.* (1979) (equation 4) is that a sensitivity term, 'm', appears in the relationship. It should therefore be possible to determine whether a given change in labetalol concentration is associated with the same change in blood pressure during and following pregnancy. In this study, the effect model successfully predicted the pattern of blood pressure change for

most women in the supine position during pregnancy and was slightly less successful in the standing position (Table 2). The fall in blood pressure in the postpartum women and normotensive volunteers was insufficient to enable any modelling to be performed. During pregnancy, systolic blood pressure was reduced by an average of 0.45 mm Hg per ng ml⁻¹ of labetalol in the supine position and 0.78 mm Hg per ng ml⁻¹ of labetalol standing.

Corresponding figures for diastolic blood pressure were 0.64 and 0.43 mm Hg per ng ml⁻¹ of labetalol. The same labetalol concentrations and rate of clearance were seen in the other two groups, but no change in blood pressure occurred. There are two possible explanations for this observation. First, the extent to which labetalol lowers blood pressure could depend on the pretreatment value of arterial pressure: higher blood pressures being associated with a greater response to labetalol. This has been observed with other drugs. For example, a given plasma concentration of clonidine produced a quantitatively greater blood pressure fall in hypertensive subjects compared to normal volunteers (Wing *et al.*, 1977). The second possible explanation is that physiological changes during the last trimester, or pathological changes associated with pregnancy associated hypertension, increase adrenoceptor sensitivity to labetalol. On the basis of the currently available evidence it is not possible to comment further on this point.

While concentration-effect modelling produced only limited information in the present study, we believe that the generally good relationships between calculated and observed blood pressure is encouraging. This approach is likely to prove useful in future studies both in the context of pregnancy and in other circumstances.

References

- BEVINGTON, P.R. (1969). *Data reduction and error analysis for the physical sciences*. New York: McGraw Hill.
- CHEN, S.-S., PERUCCA, E., LEE, J.-N. & RICHENS, A. (1982). Serum phenytoin binding and free concentration of phenytoin and phenobarbitone in pregnancy. *Br. J. clin. Pharmacol.*, **13**, 547-552.
- DAM, M., CHRISTIANSEN, J., MUNCK, O. & MYGIND, K.I. (1979). Antiepileptic drugs: metabolism in pregnancy. *Clin. Pharmacokin.*, **4**, 53-62.
- DAVIS, M., SIMMONS, C.J., DORDINI, B., MAXWELL, J.D. & WILLIAMS, R. (1973). Induction of hepatic enzymes during normal pregnancy. *J. Obstet. Gynaec. Br. Commonw.*, **80**, 690-694.
- DUNLOP, W. (1976). Investigations into the influence of posture on renal plasma flow and glomerular filtration rate during late pregnancy. *Br. J. Obstet. Gynaec.*, **83**, 17-23.
- GEORGE, C.F. (1979). Drug kinetics and hepatic blood flow. *Clin. Pharmacokin.*, **4**, 433-448.
- GRAYSON, J. & MENDEL, D. (1965). *Physiology of the splanchnic circulation*. London: Arnold.
- HOFFMAN, B.B., LAVIN, T.N., LEFKOWITZ, R.J. & RUFFOLO, R.R. (1981). Alpha adrenergic receptor subtypes in rabbit uterus: mediation of myometrial contraction and regulation by estrogens. *J. Pharmac. exp. Ther.* **219**, 290-295.

- HOPKINS, R., MARTIN, L.E., OXFORD, J. & SCULLY, N. (1978). Isolation and characterisation of glucuronide conjugates of labetalol. In *Conjugation reactions in drug biotransformation*, ed. Aito, A., p 500. Amsterdam: Elsevier Press.
- HUNTER, J. (1976). Enzyme induction and inhibition during pregnancy. In *Anticonvulsant drugs and enzyme induction*, eds Richens, A. & Woodford, B., pp 131-133. Amsterdam: Elsevier.
- HYTTEN, F.E. & LEITCH, I. (1971). *The physiology of human pregnancy*. Oxford: Blackwell Scientific Publications.
- KNUTTI, R., ROTHWEILLER, H. & SCHLATTER, C. (1981). Effect of pregnancy on the pharmacokinetics of caffeine. *Eur. J. clin. Pharmac.*, **21**, 121-126.
- KOCHENOUR, N.K., EMERY, M.G. & SAWCHUK, R.J. (1980). Phenytoin metabolism in pregnancy. *Obstet. Gynecol.*, **56**, 577-582.
- LANDER, C.M., EDWARDS, V.E., EADIE, J.J. & TYRER, J.H. (1977). Plasma anticonvulsant concentrations during pregnancy. *Neurology*, **27**, 128-131.
- LANDON, M.J. & KIRKLEY, M. (1979). Metabolism of diphenylhydantoin (phenytoin) during pregnancy. *Br. J. Obstet. Gynaec.*, **86**, 125-132.
- MEREDITH, P.A., MCHARRY, D., ELLIOTT, H.L. & REID, J.L. (1982). The determination of labetalol in plasma by high pressure liquid chromatography using fluorescence detection. *J. pharmac. Meth.*, **6**, 309-314.
- MYGIND, K.I., DAM, M. & CHRISTIANSEN, J. (1976). Phenytoin and phenobarbitone plasma clearance during pregnancy. *Acta Neurol. Scand.*, **54**, 160-166.
- PARRY, E., SHIELDS, R. & TURNBULL, A.C. (1970). Transit time in the small intestine in pregnancy. *J. Obstet. Gynaec. Br. Commonw.*, **77**, 900-901.
- RILEY, A. & SYMONDS, E.M. (1982). The investigation of labetalol in the management of hypertension in pregnancy. Amsterdam: Excerpta Medica.
- SHEINER, L.B., STANSKI, D.R., VOZEL, S., MILLER, R.D. & HAM, J. (1979). Simultaneous modelling of pharmacokinetics and pharmacodynamics: Application to d-tubocurarine. *Clin. Pharmac. Ther.*, **25**, 358-371.
- SKELLERN, G.G., KNIGHT, B.I., OTTER, M., LOW, C.K.L. & ALEXANDER, W.D. (1980). The pharmacokinetics of methimazole in pregnant patients after oral administration of carbimazole. *Br. J. clin. Pharmac.*, **9**, 145-147.
- STUDD, J.W.W., STARKE, C.M. & BLAINEY, J.D. (1970). Serum protein changes in the parturient mother, fetus and newborn infant. *J. Obstet. Gynaec. Br. Commonw.*, **77**, 511-517.
- WHITING, B. & KELMAN, A.W. (1980). The modelling of drug response. *Clin. Sci.*, **59**, 311-315.
- WING, L.M.R., REID, J.L., DAVIES, D.S., NEILL, E.A.M., TRIPPETT, P. & DOLLERY, C.T. (1977). Pharmacokinetic and concentration effect relationships of clonidine in essential hypertension. *Eur. J. clin. Pharmac.*, **12**, 463-469.

(Received October 8, 1982,
accepted December 14, 1982)