Br. J. clin. Pharmac. (1979), **8**, 157S–161S

PHARMACOKINETICS AND PHARMACODYNAMIC STUDIES OF LABETALOL IN HYPERTENSIVE SUBJECTS

J.J. McNEIL, A.E. ANDERSON & W.J. LOUIS

Clinical Pharmacology and Therapeutics Unit, University of Melbourne, Austin Hospital, Heidelberg, Victoria, Australia 3084

D.J. MORGAN

Victorian College of Pharmacy Ltd, 381 Royal Parade, Parkville, Victoria, Australia 3052

1 The pharmacokinetics of labetalol were studied in twelve hypertensive patients, ten of whom were not receiving other therapy.

2 Following intravenous administration there was a three- to fourfold variation in terminal elimination half-life, volume of distribution and total plasma clearance. The mean elimination half-life was 3.25 hours.

3 Following oral administration the drug was absorbed rapidly. Systemic availability varied from 11–86% (mean 33%).

4 Plasma levels correlated poorly with the acute effect on BP, raising the possibility of labetalol acting in a deep tissue compartment or alternatively an active metabolite contributing to its effect.

Introduction

LABETALOL (AH5158; 5 [1-hydroxy-2 [(1-methyl-3-phenyl propyl) amino] ethyl]) salicylamide; Trandate; Allen and Hanburys) is a new hypotensive drug with α- and β-adrenoceptor-blocking activity (Farmer *et al.*, 1972; Collier *et al.*, 1972).

The drug is a modification of conventional β-adrenoceptor-blocking drugs in which the isopropyl group has been replaced by an alkyl substitution and there is a salicymide moiety on the aromatic terminus. It has two optical centres and four possible diastereoisomers. There are no published data on the relative antihypertensive effects of the various isomers. Limited acute pharmacokinetic studies have been reported (Martin *et al.*, 1976; Richards *et al.*, 1977; Louis *et al.*, 1978), suggesting variable bioavailability. The present report is a detailed study of the pharmacokinetics of labetalol following acute single dose administration of 100 and 200 mg.

Methods

Seven males and five females with mild to moderate hypertension, aged 21–65 yr (mean 49.9 yr) and weighing 55–99 kg (mean 76.6 kg) were studied. Five patients had received no antihypertensive treatment, and the other seven had been treated for periods ranging from 1–10 yr but were transferred to placebo for at least 8 weeks before the first study. One patient had renovascular hypertension with normal renal function. In the remainder secondary forms of hypertension were excluded by previous investigation. Hepatic and renal function were normal in all patients.

Casual BPs taken before the commencement of the study ranged from 130/95 mmHg to 165/120 mmHg with a mean of 161/105 mmHg. All subjects had a normal chest X-ray without evidence of cardiomegaly. Nine had normal electrocardiograms and in the remainder the abnormalities consisted of minor ST segment and T wave changes.

Ten patients were receiving no medication apart from their antihypertensive drugs. One was receiving ibuprofen 800 mg daily and the other indomethacin 100 mg daily plus nitrazepam. These drugs were withheld for 3 d before each study. In addition all subjects agreed to avoid over-the-counter medication for at least 3 d before each investigation and to abstain from alcohol from 48 h before until after the completion of each study.

Each patient received labetalol 100 mg intravenously on the first occasion and 100 mg or 200 mg orally on the other. On the morning of each study patients attended at 0800 having fasted for 8 hours. A venous cannula was inserted into a forearm vein and kept patent with normal saline containing heparin 40

0306–5251/79/170157–05 $01.00

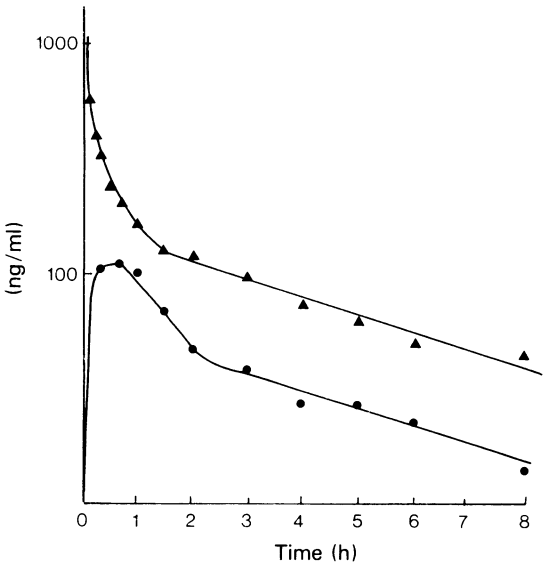

Figure 1 Semilogarithmic plot of mean plasma labetalol concentration after administration of 100 mg intravenously (▲) to twelve patients and orally to six patients (●).

U/ml. Subjects then rested in the supine position for 30 min before baseline physiological measurements were made and baseline blood samples drawn.

Oral medication was administered as 100 mg tablets taken with 100 ml water. Intravenous labetalol was infused for 2 min into the arm opposite to that used for sampling; 20 ml of a solution containing 5 mg/ml was administered.

Nothing was eaten until 4 h after drug administration when a meal of three sandwiches was taken. Free intake of water was allowed after 4 hours. Before drug administration an initial blood sample was taken as a plasma blank. With the oral studies 7 ml blood samples were collected into heparinized blood collection tubes at 20, 40 and 60 min and at 1.5, 2, 2.5, 3, 4, 5, 6 and 8 h after drug administration. After intravenous administration the corresponding intervals (time from the end of infusion) were 5, 7, 10, 15, 20, 30, 45 and 60 min and 1.5, 2, 3, 4, 5, 6 and 8 hours. The plasma was separated within 10 min of collection, then frozen and kept at −15°C until analyzed.

Physiological measurements

Supine BP was determined using a conventional sphygmomanometer (taking Phase 4 of the Kortkoff sounds as the diastolic BP) and measured at the time of the sample collection in each study. Measurement of upright BP and pulse rate taken after 2 min standing was recorded during each oral dose study.

Chemical analysis

Plasma samples of labetalol were determined using a spectrofluorimetric procedure. Using 1 ml plasma the sensitivity of the assay was approximately 20 ng/ml (Richards *et al.*; 1977).

Pharmacokinetic analysis

The observed post-infusion concentration time data for each subject were analyzed using a decision-making least-squares regression analysis program (AUTOAN) in order to fit first-order exponential decay equations of the type:

$$Cp = A' e^{-\alpha t} + B' e^{-\beta t} \quad (1)$$

or

$$Cp = P' e^{-\pi t'} + A' e^{-\alpha t'} + Be^{-\beta t'} \quad (2)$$

where Cp is the post-infusion plasma concentration at time t' after completion of the infusion and π, α and β are the first-order exponential rate constants for the fast, medium and slow disposition processes respectively. P', A' and B' are the ordinate intercepts of the exponential terms at $t' = 0$. P, A and B are the predicted values of the ordinate intercepts had the drug been given as a bolus injection and were calculated by the method of Loo & Riegelman (1970).

The coefficients and exponents of equations (1) and (2) were used to calculate the initial distribution volume (V_1), the total apparent volume of distribution at equilibrium (Vd_β), the terminal elimination half-life ($T\frac{1}{2}\beta$) and total plasma clearance by standard methods (Gibaldi & Perrier, 1975).

Following oral dosing the area under the plasma concentration–time curve (AUC) was calculated to the time (t) of the last measured plasma concentration using the trapezoidal method and from this time to infinity using the expression Ct/β, where β is the slope of the terminal elimination phase derived from the intravenous administration of labetalol to the same subject. Following intravenous administration the AUC was calculated from the expression:

$$\text{AUC} = \frac{P}{\pi} + \frac{A}{\alpha} + \frac{B}{\beta}$$

Results

Intravenous study

Plasma concentrations of labetalol following 2 min infusion of the drug are shown in Fig. 1 as semilogarithmic plot of mean values, together with

those of the corresponding 100 mg oral dose. The intravenous plasma concentration data from six patients was fitted best by the biexponential equation (1) and the other six by the triexponential equation (2).

The kinetic parameters for labetalol following intravenous administration are summarized in Table 1. Plasma levels immediately following the infusion were variable, as reflected by the tenfold variation in the initial distribution volume. At pharmacokinetic equilibrium the total apparent volume of distribution ranged from 188 to 746 l (mean 393 l) and individual values correlated poorly with body weight and surface area. A similar degree of variability was present in the terminal elimination half-life, which varied from 1.7–6.1 hr with a mean value of 3.25 hours. The total plasma clearance was 1500 (± 163 s.e.m.) ml/minute. During the study two patients complained of parasthesiae of the scalp but no other untoward effects were noted.

Oral study

Following labetalol 100 mg and 200 mg orally, the drug was absorbed rapidly, with peak levels occurring 20–60 min after the 100 mg dose and later to a significant extent after the 200 mg dose (40–90 min, $P < 0.01$). The magnitude of the peak levels ranged from 96–250 ng/ml after 100 mg (mean 157) and from 93–271 ng/ml (mean 191) after 200 mg (Table 2).

From peak levels the plasma concentrations fell in a biexponential fashion, with a secondary peak following food being recognizable in five patients. Because of these fluctuations, a terminal elimination phase could not be characterized.

The systemic availability of the orally administered

Table 1 Kinetic parameters of labetalol disposition following intravenous administration

Patient no.	Exponent	*Fit (R^2)	V_1 (*l*)	$V_{2nd}\beta$ (*l*)	Vd/kg (*l/kg*)	$T_{\frac{1}{2}}$ elim. (*h*)	AUC (*ng/ml/h*)	Plasma clearance (*ml/min*)
1	2	0.983	69.6	747	10.7	4.75	918	1815
2	2	0.995	28.4	364	4.6	2.90	1150	1450
3	2	0.999	42.7	410	5.6	3.05	1072	1554
4	3	0.995	15.1	433	6.7	3.62	1206	1382
5	3	0.999	7.7	188	3.4	3.22	2470	675
6	3	0.997	8.4	254	3.7	3.74	2128	783
7	2	0.993	70.4	426	4.6	1.99	675	2471
8	3	0.998	19.7	513	5.2	2.72	765	2178
9	2	0.984	43.2	266	3.7	1.70	923	1806
10	2	1.000	19.7	257	3.7	2.25	1263	1319
11	3	0.997	35.2	458	4.6	2.92	921	1809
12	3	0.995	15.1	402	5.1	6.13	2204	756
$\bar{X}$			31.3	393	5.13	3.25	1308	1500
$s\bar{X}$			6.26	43.0	0.58	0.35	175	163

*Measure of "goodness of fit" (Sedman & Wagner, 1974).

Table 2 Summary of plasma level data following oral administration

Patient no.	*Dose (mg)*	*Peal level (ng)*	*Time to peak (min)*	*AUC (ng/ml/h)*	*Systemic availability*
1	100	228	20	786	86
2	100	250	60	454	40
3	100	100	40	455	42
4	100	96	20	344	29
5	100	141	20	277	11
6	100	125	40	467	22
$\bar{X}$		157	33	462	38
$s\bar{X}$		27	7	72	11
7	200	240	90	662	49
8	200	135	60	414	27
9	200	196	60	550	30
10	200	93	90	252	30
11	200	212	40	395	21
12	200	271	60	820	19
$\bar{X}$		191	67	516	28
$s\bar{X}$		27	8	84	5

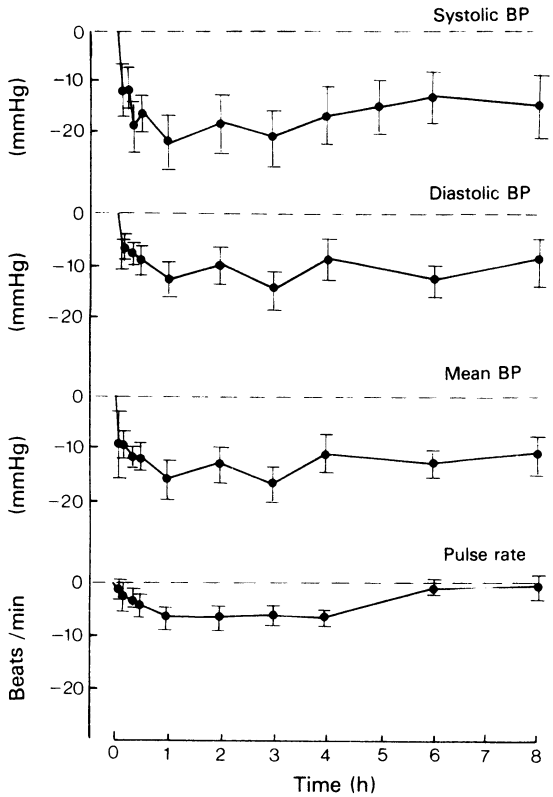

Figure 2 Average fall in supine BPs (systolic, diastolic and mean) and pulse rate in twelve patients at various times after receiving labetalol 100 mg intravenously.

drug varied from 11–86% after the 100 mg dose and from 19–49% after the 20 mg dose. The mean values were not significantly different (unpaired *t* test). The overall mean systemic availability was 33%.

Pharmacodynamics

The intravenous administration of labetalol 100 mg (Fig. 2) produced an immediate effect on mean systolic and diastolic BPs, which fell from 152 ± 6 mmHg systolic and 99.4 ± 3 mmHg, respectively, 5 min after the infusion. Following the initial fall, mean BP continued to drop reaching a minimum level of 131 ± 4 systolic and 85 ± 3 diastolic at 3 hours. A substantial hypotensive effect persisted during the remainder of the 8 hr observation period. There was no correlation between individual values of area under plasma concentration–time curves and areas under mean BP fall–time curves.

Following oral administration of 100 mg of the drug there was a maximal fall in mean BPs of 29 mmHg systolic and 9 mmHg diastolic and a maximal fall in mean standing BPs of 28 mmHg systolic and 14 mmHg diastolic.

Following the 200 mg oral dose the maximal fall in mean supine BPs was 23 mmHg systolic and 27 mmHg diastolic mmHg at 6 hr, and with upright BPs the maximal fall was 23 mmHg systolic and 22 mmHg diastolic at 3 hours. Over an 8 hr period the cardiovascular effects of both 100 and 200 mg doses were better maintained than the plasma concentration of the drug. Mean peak plasma levels occurred at 33 min for the 100 mg dose and 67 min for the 200 mg dose, and did not correlate with the magnitude of the BP fall expressed as the area under the supine BP against time curve during the first 8 hr after labetalol administration. There was also no correlation between bioavailability and the BP response.

There was an inverse correlation between maximum fall in diastolic BP and labetalol level 5, 10 and 15 min after intravenous infusion ($r = 0.70$, $P < 0.01$ for 5 min data; $r = 0.77$, $P < 0.01$ for 10 min data; $r = 0.73$, $P < 0.01$ for 15 min data; $r = 0.67$, $P < 0.05$ for 30 min data; $r = 0.61$, $P < 0.05$ for 45 min data).

Discussion

The present study confirms previous reports in humans which have shown that labetalol is a drug characterized by considerable variation in bioavailability (Louis *et al.*, 1978; Homeida *et al.*, 1978). The drug is believed to undergo hepatic biotransformation with only 5% of unchanged drug recoverable in urine (Martin *et al.*, 1976). In these respects it resembles other highly metabolized β-adrenoceptor-blocking agents, such as propranolol, metoprolol and alprenolol. It is, however, less lipophilic than propranolol, and little enters brain tissue (Martin *et al.*, 1976). After the administration of the radiolabelled drug, high levels of radioactivity have been found in liver, lung and kidney (Martin *et al.*, 1976).

Following intravenous administration there was a three- to four-fold variation in terminal elimination half-life, volume of distribution and total plasma clearance. The mean half-life was 3.25 hr (± 1.22 s.e.m), a value in close agreement with that reported in normal volunteers (Homeida *et al.*, 1978). The high plasma clearance (1500 ml/min ± 564 s.e.m.) suggests extensive hepatic binding and biotransformation, and the large volume of distribution (Vd_β) is compatible with extensive tissue uptake.

After oral administration peak levels were reached as early as 20 min after injection, which suggests that significant proportions of the drug are absorbed in the stomach. Similar rapid absorption has been

described for alprenolol, oxprenolol and metoprolol. In the case of labetalol this rapid absorption can be associated with symptoms of postural hypotension (Louis *et al.*, 1978a; Louis *et al.*, 1978b) and in most clinical situations the drug is best given in divided doses.

Unlike other β-adrenoceptor-blocking drugs, labetalol causes a significant fall in BP following single doses of the drug given either intravenously of orally (Koch 1976; Ghose *et al.*, 1978). After the intravenous dose there was a significant effect on both systolic and diastolic BPs within 5 minutes. Thereafter a further fall in BP took place with a maximal lowering of the mean BP occurring between 1–3 hours. The duration of the hypotensive effect was longer than would be expected from the profile of the plasma concentration–time curve.

Following the 100 mg oral dose the maximal lowering of mean supine and standing BPs took place at 1 h but after the 200 mg oral dose the maximal effect was delayed until 3 hr in the standing position and 6 hr in the supine position. Again, at the higher dose, the time course of the effect on BP bore little resemblance to the profile of the plasma concentration–time curve. In addition there was a poor correlation between the areas under the plasma concentration–time curve and the corresponding area under the BP fall–time profile. Peak levels also did not correlate with maximal effect on BP. It was of interest, however, that the fall in plasma labetalol levels during the first hour after intravenous administration was inversely related to subsequent maximal fall in supine diastolic BP. This suggests that the more rapid the distribution the greater the effect on BP. These observations therefore raise the possibility of labetalol acting at deep tissue compartment or alternatively an active metabolite contributing to its effect.

This work was supported by a grant from the Life Insurance Fund of Australia and New Zealand. The helpful advice of Dr K. Raymond (Victorian College of Pharmacy Ltd) is gratefully acknowledged.

References

COLLIER, J.G., DAWNAY, N.A.H., NACHEV, C.H. & ROBINSON, B.F. (1972). CLinical investigation of an antagonist at α- and β-adrenoreceptors. AH 5158A. *Br. J. Pharmac.*, **44**, 286–293.

FARMER, J.B., KENNEDY, J., LEVY, G.P. & MARSHALL, R.J. (1972). Pharmacology of AH5158; a drug which blocks both α- and β-adrenoreceptors. *Br. J. Pharmac.*, **45**, 660–675.

GHOSE, R.R., MATHUR, Y.B., UPADHYAY, M., MORGAN, W.D. & KHAN, S. (1978). Treatment of hypertensive emergencies with oral labetalol. *Br. J. Pharmac.*, 96.

GIBALDI, M. & PERRIER, D. (1975). *Pharmacokinetics*. New York: Marcel Dekker.

HOMEIDA, M., JACKSON, L. & ROBERTS, C.J.C. (1978). Decreased first-pass metabolism of labetalol in chronic liver disease. *Br. med. J.*, **2**, 1048–1050.

KOCH, G. (1976). Combined α- and β-adrenoreceptor blockade with oral labetalol in hypertensive patients with reference to haemodynamic effects at rest during exercise. *Br. J. clin. Pharmac.*, suppl. 729–732.

LOO, J.C.K. & REIGELMAN, S. (1970). Assessment of pharmacokinetic constants from post-infusion blood curves obtained after intravenous infusion. *J. Pharm. Sci.*, **59**, 53–55.

LOUIS, W.J., BRIGNELL, M.J., McNEIL, J.J., CHRISTOPHIDIS, N. & VAJDA, F.J.E. (1978a). Labetalol in hypertension (Letter). *Lancet*, **i**, 452–453.

LOUIS, W.J., CHRISTOPHIDIS, N., BRIGNELL, M., VIJAYASEKARAN, V., McMEIL, J. & VAJDA, F.J.E. (1978b). Labetalol: bioavailability, drug plasma levels, plasma renin and catecholamines in acute an chronic treatment of resistant hypertension. *Aust. N. Z. J. Med.*, **8**, 602–609.

MARTIN, L.E., HOPKINS, R. & BLAND, R. (1976). Metabolism of labetalol by animals in man. *Br. J. clin. Pharmac.*, suppl. 695–710.

RICHARDS, D.A., MACONOCHIE, J.G., BLAND, R.E., HOPKINS, R., WOODINGS, E.P. & MARTIN, L.E. (1977). Relationship between plasma concentrations and pharmacological effects of labetalol. *Eur. J. clin. Pharmac.*, **11**, 85–90.

SEDMAN, H.A. & WAGNER, J.G. (1974). *AUTOAN: A Decision-Making Pharmacokinetic Computer Program*. Ann Arbor, Michigan: Publication Distribution.