found that some 30% and 56% of the dose of radioactivity was excreted in urine during 24 and 144 h respectively after dosing. These workers estimated that about 80% of the urinary radioactivity was unchanged metolazone and thus some 24% and 45% of the administered drug was excreted unchanged in these time periods. The recovery of metolazone in urine during 24 h in the present study is thus similar to that reported by Tilstone *et al.* (1974).

During the development of the fluorimetric assay a number of techniques were investigated in an attempt to reduce the fluorescence background caused by endogenous components in the urine extracts and thus increase the sensitivity of the assay method. These techniques included acid and alkali back extraction procedures similar to those described for hydroflumethiazide (Brors, Jacobsen & Arnesen, 1977) and pre-extraction of the biological fluids with hexane. However, none of these modifications appeared to increase the sensitivity of the assay.

In view of this the most likely way of improving this fluorimetric assay would be to combine the fluorimetric quantitation technique with liquid chromatography. The addition of the separation technique should lower or eliminate the background

(blank) fluorescence from endogenous compounds, thereby improving the overall sensitivity of the assay.

C.W. VOSE, P.M. STEVENS, D.C. MUIRHEAD,
R.F. PALMER & G.T. McINNES

Department of Metabolic Studies, G.D. Searle & Co Ltd, Lane End Road, High Wycombe, Bucks

Received October 17, 1979

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PHARMACOKINETICS OF ACEBUTOLOL AFTER INTRAVENOUS BOLUS ADMINISTRATION

Acebutolol is a β -adrenergic receptor blocking agent (Kumana, Kaye, Leighton, Turner & Hamer, 1975), which has been shown to be clinically effective in the treatment of hypertension (Lucsko, Chaignon & Guedon, 1975). Pharmacokinetics of acebutolol have been studied by Meffin, Winkle, Peters & Harrison, 1977, at different dosages (0.25 to 1 mg/kg) after intravenous infusion. The present investigation was to determine pharmacokinetics after an intravenous bolus.

Five healthy male volunteers (age range 29–46 years, weight range 65–82 kg), all of whom had no history of asthma, had normal ECG, and normal biological constants (creatinine, urea, transaminases, bilirubin, proteins, haematocrit), participated in the study after giving informed consent. After overnight fasting, each subject received 0.35 mg/kg acebutolol bolus (D), which was injected via a forearm antecubital vein, over 1 min. Blood samples were taken, on dry heparin, from the contralateral forearm, at 2, 4, 7, 10, 15, 30, 45, 60, 90, 120 min and 3, 4, 6, 8, 12 and 24 h after the end of the injection. Blood samples were centrifuged and plasma separated prior freezing at -20°C until analysis. Urine was collected from 0–2, 2–4, 4–6, 6–8, 8–12, 12–24, 24–48 and

48–72 h; urine volumes were measured and aliquots of each portion were frozen until assayed.

Concentrations of acebutolol and N-acetyl metabolite in blood and urine were measured using a specific high-pressure liquid chromatographic method (Gulaid, Lewellen & Sankey, personal communication, modified by Roux & Flouvat, 1978).

The plasma results were fitted to three exponential functions of the type ($A_1e^{-\alpha t} + A_2e^{-\beta t} + A_3e^{-\gamma t}$) using a non-linear least squares regression analysis program. The different constants of this equation are shown in Table 1 and illustrated for one subject in Figure 1. Plasma levels were undetectable after the tenth hour. A three open compartment model was chosen (Figure 2) and the corresponding microscopic rate constants, volumes of distribution, total body clearance, and elimination rate constant were calculated (Gibaldi & Perrier, 1975) (Table 1).

The mean plasma half-life of the terminal phase (2.67 ± 0.48 h) is in good agreement with that observed by Meffin *et al.* (1977) (2.6 h). After oral administration of 200 mg to ten healthy subjects, analysis of plasma concentrations during the same time as i.v. (10 h) showed a half-life of 4.1 h close to the i.v. value (Roux, Aubert, Guedon & Flouvat,

Figure 1 Semilogarithmic plot of acebutolol plasma concentrations following intravenous administration of 0.35 mg/kg acebutolol to subject 4. The inset is for an expanded time scale.

Figure 2 Pharmacokinetic model for intravenous administration of acebutolol.

1980). A slow phase of elimination was also apparent ($T_{1/2}$ 8.8 h). The elimination rate constant ($k_{el} = 3.83 \pm 1.74 \text{ h}^{-1}$) was significantly higher ($P < 0.02$) than that observed by Meffin *et al.* (1977) which was $2.07 \pm 0.83 \text{ h}^{-1}$. This discrepancy may be explained by the difference in methodology, a 15 min infusion (Meffin *et al.*, 1977) compared with a 1 min bolus in our study, that allowed us to use a three compartment open model and consequently to find a higher C_0 value ($C_0 = A_1 + A_2 + A_3$). This term, C_0 , enters in k_{el} formula ($k_{el} = C_0 / \text{AUC}_{0-\infty}$).

The volume of distribution of the central compartment ($11.1 \pm 4.9 \text{ l}$), was smaller than that observed by Meffin *et al.* (1977) (28.1 l after correction for haematocrit and blood cell binding as

Table 1 Acebutolol pharmacokinetic parameters

Subjects	1	2	3	4	5	Mean	s.d.
A_1 ($\mu\text{g l}^{-1}$)	941	2158	2687	3917	1384	2218	1166
α (h^{-1})	16.82	22.46	22.73	34.92	19.74	23.33	6.90
A_2 ($\mu\text{g l}^{-1}$)	262	233	436	585	220	347	159
β (h^{-1})	3.457	2.763	3.080	4.139	2.439	3.175	0.657
A_3 ($\mu\text{g l}^{-1}$)	135	144	162	140	85	133	29
γ (h^{-1})	0.224	0.333	0.229	0.309	0.236	0.266	0.051
C_0 ($\mu\text{g l}^{-1}$)	1346	2536	3286	4642	1689	2700	1323
k_{el} (h^{-1})	1.82	4.12	3.39	6.55	3.25	3.83	1.74
$T_{1/2}$ (h)	3.09	2.08	3.03	2.24	2.93	2.67	0.48
$\text{AUC}_{0-\infty}$ ($\mu\text{g h l}^{-1}$)	739	616	969	709	519	710	168
V_1 (l)	18.3	10.3	7.3	6.2	13.5	11.1	4.9
V_2 (l)	14.9	18.5	7.0	10.4	21.8	14.5	6.0
V_3 (l)	90.1	64.2	41.0	69.7	96.3	72.3	22.0
$k_{1,2}$ (h^{-1})	5.63	9.30	9.18	14.48	8.48	9.42	3.20
$k_{2,1}$ (h^{-1})	6.94	5.21	6.28	8.58	5.24	6.45	1.40
$k_{1,3}$ (h^{-1})	5.07	5.96	6.44	8.96	4.77	6.24	1.66
$k_{3,1}$ (h^{-1})	1.03	0.96	0.75	0.79	0.67	0.84	0.15
k_u (h^{-1})	0.59	0.94	1.07	2.26	1.10	1.19	0.63
Cl_t (ml min^{-1})	550	710	412	675	730	615	133
Cl_u (ml min^{-1})	180	162	132	232	247	190	48

indicated by authors), because in our study, blood samples were drawn as soon as 2 min after bolus end.

The total body clearance ($Cl_t = 615$ ml/min) showed that elimination occurred by the extra-renal as well as renal routes. Renal clearance ($Cl_u = 190$ ml/min) represents one-third of total clearance. This value is in good agreement with urine elimination of unchanged drug measured as % of drug injected ($30.3 \pm 4.4\%$ during the first 24 h and $30.8 \pm 4.5\%$ in 72 h). The urine elimination of acetylmabolite is $14.9 \pm 3.3\%$ in 24 h and $17.9 \pm 4.0\%$ in 72 h (% of drug injected, corrected for molecular weight).

The volume of tissue distribution ($V_3 = 1.0$ l/kg) of acebutolol is the lowest of β -adrenoceptor-blockers; it is comparable with atenolol (1.3 l/kg, Mason, Winer, Kochat, Cohen & Bell, 1979), oxprenolol (1.3 l/kg, Mason & Winer, 1976) and practolol (1.6 l/kg, Bodem & Chidsey, 1973); metoprolol has the highest V_3 (5.6 l/kg, Regardh, Borg, Johansson, Johnsson & Palmer, 1974).

In conclusion, acebutolol pharmacokinetic analysis, after a bolus infusion, can be described as a three open compartment model.

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A. ROUX & B. FLOUVAT

Département de Pharmacologie Clinique, Laboratoire de Toxicologie, Hôpital Ambroise Paré, 9 avenue Charles de Gaulle, 92100 Boulogne Sur Seine, France

N.P. CHAU

U.E.R. Saint Quentin, France

B. LETAC

Service de Cardiologie, Hôpital Ch. Nicolle, Rouen, France

M. LUCSKO

Service de Néphrologie (Docteur Guedon), CMC Foch, Suresnes, France

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CONTROLLED TRIAL OF METOCLOPRAMIDE IN THE INITIATION OF BREAST FEEDING

The superiority of breast milk for the health of the human neonate is unchallenged. However, many women do not succeed in breast feeding and abandon it early because of anxiety that the child is not being adequately fed. It is not clear how many of these women have a genuinely inadequate supply of milk but it would be an advantage if some means existed of

increasing milk production temporarily. Increasing prolactin secretion might be a possible approach.

Synthetic thyrotropin releasing hormone (TRH, Roche) stimulates prolactin release (Jeppsson, Nilsson, Rannevik & Wide, 1976) and increases milk production in lactating women (Tyson, Khojandi, Huth & Andreasson, 1975; Zarate, Villalobos,