Mixed linear and non-linear disposition of lazabemide, a reversible and selective inhibitor of monoamine oxidase B

T. W. GUENTERT¹, N. H. G. HOLFORD², J. P. PFEFEN¹ & J. DINGEMANSE¹

¹Department of Clinical Pharmacology, F. Hoffmann-La Roche Ltd, CH-4002 Basel, Switzerland and ²Department of Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand

- 1 Single oral doses (100–300 mg) and multiple oral doses (100–350 mg 12 hourly for 7 days) of lazabemide were administered to 35 young and 40 elderly healthy subjects. Plasma concentrations of unchanged drug were determined to study the dose-concentration relationship.
- 2 The elimination phase time course of lazabemide concentrations indicated concentration-dependent elimination after both single and multiple dosing. Nevertheless, maximum concentrations and areas under concentration-time curves increased almost proportionally with dose and accumulation after chronic dosing was less than a factor of 2; steady-state concentrations were achieved by the third day of dosing. The apparent half-life determining accumulation was approximately 8–9 h.
- 3 Drug absorption commenced rapidly after a dose; two components to the absorption process were detectable in young subjects possibly due to simultaneous administration of multiple tablets at the higher doses.
- 4 Observations after single and multiple dosing were described with a compartmental model allowing for parallel saturable (population mean $\pm$ s.d.: maximum elimination rate $V_{\max}/F$: 2.8 ± 1.4 mg h⁻¹; concentration at half-maximum elimination K_m : 36 ± 19 μ g l⁻¹) and first-order (CL/F 16 ± 3.8 l h⁻¹) elimination pathways. No important difference between the young and the elderly subjects was noted in absorption or disposition parameters of lazabemide.

Keywords lazabemide Ro 19-6327 MAO-inhibition population pharmacokinetics modelling

Introduction

Monoamine oxidases (MAO) are mitochondrial enzymes found in most mammalian tissues and are classified into type A and type B according to substrate specificity [1]. Owing to their involvement in the degradation of neurotransmitter amines (e.g. MAO-A: serotonin, adrenaline, noradrenaline, dopamine; MAO-B: dopamine) inhibitors of these enzymes are clinically used or are being evaluated in the treatment of a number of diseases of the central nervous system. While MAO-A inhibitors are primarily used in the treatment of depression and certain phobic-anxiety states, MAO-B inhibitors are thought to be useful in Parkinson's disease as an adjunct to levodopa therapy or to slow down the progression of the disease [2].

Lazabemide (*N*-(2-aminoethyl)-5-chloro-2-pyridine-

carboxamide; Ro 19-6327) is an investigational, selective and reversible inhibitor of MAO-B [3]. During single- and multiple-dose tolerability studies in young and elderly volunteers, plasma concentrations and inhibition of platelet MAO-B activity were determined to obtain initial information on the drug in humans and to enable studies on the relationship between dose, drug concentrations and drug effects. The results from two different studies are reported. The first included healthy young subjects receiving single doses of 100–300 mg. In the second study elderly subjects received active drug for 7 days at doses of 100 to 350 mg every 12 h. This report describes the search for a model to describe the dose-concentration relationship and the population pharmacokinetic parameters of the most satisfactory model.

Methods

Clinical studies

The clinical studies were carried out according to the principles laid down in the Declaration of Helsinki following approval of the Institutional Ethics Committee and written informed consent from the subjects. All volunteers understood that they were free to withdraw from the study at any time.

Both clinical studies reported were designed as fixed sequence ascending dose, double-blind, parallel group investigations with placebo control because pharmacological effects were also recorded. Prior to enrolment in the study, subjects underwent a physical examination and laboratory tests. Volunteers were excluded if these tests were abnormal, if they smoked more than 10 cigarettes/day, if they had a significant food or drug allergy or if they had any history of drug abuse or drug intolerance.

Subjects were admitted to the clinical research centre in the evening before the first drug administration. After an overnight fast they received drug or matching placebo at 08.00 h together with 150–200 ml water. After the first (and, in the case of the multiple dose study, also the last) administration of the test medication the volunteers fasted for at least a further 4 h. They did not lie down until 4 h after dosing except for the evaluation of vital signs and ECG recordings unless adverse events required a supine position.

Single-dose study

Thirty-six male volunteers between 19 and 36 years old and within $\pm 15\%$ of ideal body weight (mean 78 kg, range 59–99 kg) were assigned to one of six active dose levels (100, 150, 200, 220, 250, 300 mg). Three different tablet formulations (20, 50, 100 mg) were combined to achieve the designated active drug dose. Blood (10 ml) was collected before and after drug administration (0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24, 32, 48 h). Subjects remained in the clinical research centre under medical observation until 32 h after drug administration and returned for post-study screening and the last blood sample at 48 h.

Multiple-dose study

Twenty-one male and 19 female volunteers between the ages of 60 and 78 years and within -15 to $+25\%$ of ideal body weight (mean 73 kg, range 52–99 kg) participated in the study. Intake of medication commonly used by an elderly population was allowed during the study. Dose alterations were avoided during the study period as far as possible. However, subjects requiring medication with a pronounced effect on the central nervous system or with an expected influence on the pharmacokinetics of other drugs (e.g. enzyme inhibitors/inducers, high doses of antacids) were excluded from the study. Groups of eight subjects were administered one of five active drug doses (100, 150, 200, 250, 350 mg) on the

morning of day 1 and then twice a day (08.00 h, 20.00 h) for 7 days starting 48 h after the initial dose (days 3–9). The last dose was given in the morning of study day 10. Two different (same as single dose study) tablet formulations (50, 100 mg) were used. Serial blood samples of 10 ml were collected after the morning doses on days 1 and 10 (pre-dose; 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48 h post-dose) and additional samples were obtained before the morning doses on days 5, 7 and 9. Subjects were admitted during the entire study period until 72 h after the last dose.

Blood collection procedure

Blood samples were collected via an indwelling venous catheter or by venipuncture into polypropylene tubes containing EDTA as anticoagulant. Samples were centrifuged (3000 *g* for 10 min at 4° C) within 30 min of collection and the plasma was stored at -20°C until analyzed for unchanged drug.

Chemical analyses

For determination of lazabemide 1 ml plasma was combined in a glass tube with 50 μl of a solution containing the internal standard (0.4 μg bromo-analogue of lazabemide ml^{-1}) in 0.4 *N* NaOH. After extraction (head over head 300 rev min^{-1} ; 15 min) with 10 ml *t*-butyl-methyl ether/1-butanol (8:2, v:v), the organic phase (approximately 9 ml) was transferred into another glass tube containing 350 μl of diluted phosphoric acid (1 ml *o*-phosphoric acid 85% w/v in 500 ml water). Back-extraction and centrifugation was then followed by a quantitative transfer of the acidic phase into a new glass tube avoiding carry-over of the organic phase. After addition of 30 μl of a sodium phosphate buffer (225 ml 1 *N* NaOH + 275 ml of an aqueous solution containing per litre: 20 g Na_2HPO_4 and 2.9 g NaH_2PO_4 , pH 7.4), 200 μl of fluorescamine solution (0.5 mg fluorescamine/10 ml acetonitrile) were added slowly under constant mixing. After evaporation of the acetonitrile *in vacuo* at 40° C, 270 μl of the remaining solution was injected into an h.p.l.c. system.

Chromatographic separation of lazabemide from internal standard and interfering peaks was achieved with a Lichrocart Superspher 100 RP-18e cartridge (250 $\times$ 4 mm i.d., Merck) kept at a constant temperature of 60° C. The mobile phase (flow rate: 1.3 ml min^{-1}) was a mixture of 744 g aqueous buffer solution (18.4 g NaH_2PO_4 l^{-1} water adjusted to pH 5.45 with 1 *N* NaOH), 204 g acetonitrile, 38.4 g tetrahydrofuran. The column effluent was monitored by a Waters 470 fluorescence detector (λ excitation 370 nm, emission 485 nm).

Along with every batch of study samples, calibration samples (0.5–1000 $\mu\text{g l}^{-1}$) prepared daily by spiking drug-free plasma and aliquots of quality control samples (1, 4, 40, 400, 1000 $\mu\text{g l}^{-1}$) prepared in sufficient volume before the entire analytical period were analyzed.

Concentrations in quality control and study

samples were calculated from the calibration curve using peak height ratios of active drug/internal standard. Concentrations in study samples were accepted only if results from a minimum of 75% of quality control samples deviated less than 15% from their known true value. Samples with drug concentrations above $1000 \mu\text{g l}^{-1}$ were diluted with drug-free plasma and reanalyzed.

The minimum quantifiable concentration of lazabemide was $1 \mu\text{g l}^{-1}$ with an inter-day coefficient of variation ranging from 4% ($1000 \mu\text{g l}^{-1}$) to 12% ($1 \mu\text{g l}^{-1}$).

Pharmacokinetic models

Absorption was modelled by either a single input or two sequential inputs with a lag-time prior to the start of each input. Each input process was tested as either a first-order or zero-order process. Disposition was described by distribution into one or two compartments with elimination from the central compartment by a concentration-dependent (Michaelis-Menten, mixed order) process either alone or in combination with a parallel first-order elimination pathway. The possible model parameters included a lag-time (t_{lag}) and duration of zero-order input (T_{K0}) or first-order absorption rate constant for each input; the fraction of the dose absorbed by the initial process (f_1); inter-compartmental clearance (CL_{ic}) and volume terms (V_1 , V_2) for distribution; maximum elimination rate (V_{max}), concentration at half-maximal elimination (K_m) and first-order clearance (CL) for elimination. V_{ss} was calculated from the sum of V_1 and V_2 . The general model is depicted in Figure 1.

Multiple dose accumulation was predicted from the results of the single dose study (Table 2). Concentrations after 15 doses given at 12 h intervals were obtained from a simulation using the mixed-order elimination model (single zero-order input into a single compartment without lag-time). From these concentrations the AUC(0,12) was calculated and compared with the AUC(0,12) obtained from observed concentrations after the first dose.

Figure 1 Pharmacokinetic model tested for description of the absorption and disposition of lazabemide after single and multiple dosing (t_{lag} : lag-time; T_{K0} : duration of zero-order input; k_a first-order absorption rate constant; f_1 = fraction of the dose absorbed by process 1; V_1/V_2 : volumes of central/peripheral compartment; CL_{ic} : inter-compartmental clearance; V_{max} : maximum elimination rate; K_m : concentration at $V_{\text{max}}/2$; CL: first-order elimination clearance).

Parameter estimation

Models were defined and parameters estimated using MKMODEL [4]. Differential equations were solved using a variable 4th/5th order Runge-Kutta method [5] with a relative local error tolerance of 10^{-6} to 10^{-12} . The variance of the i th measured lazabemide concentration was predicted using a power variance model:

$$\text{Var}_i = \text{SD}^2 \cdot (\hat{Y}_i^{\text{PWR}} + V_0)$$

where SD is a scale factor for the error, $\hat{Y}_i$ is the i th model prediction and V_0 the background variance. The power coefficient PWR was set to a constant with value 2.

Model discrimination

Models of different structure and complexity were assessed by inspection of graphs of predictions and observations. With models that produced similar goodness of fit by visual criteria, the Schwarz criterion [6] was used to determine the most parsimonious model.

Non-compartmental parameters

Maximum concentration (C_{max}) and the time of its occurrence (t_{max}) were determined directly from the observed time-concentration profile. Owing to the non-linear appearance of the concentration profile (Figures 2, 3) terminal half-lives were not calculated. The area under the time-concentration curve from 0 to 12 or 24 h (AUC(0,12), AUC(0,24)) was calculated from the observed concentrations by the linear trapezoidal rule. Concentrations could not be measured after 24 h following 100 mg single doses; with higher doses 24 h concentrations were close to the quantitation limit and samples collected 32 h after drug administration were unmeasurable. Only after 300 mg single and 200 mg multiple doses could concentrations be regularly measured up to 32–36 h. The accumulation behaviour of the drug after multiple dosing was determined by comparing C_{max} and AUC(0,12) after the first dose to the respective values after the last dose during the multiple dosing study. Using the resulting accumulation factors (R_{ac}) the drug's apparent half-life determining accumulation ($t_{1/2,\text{app}}$) was calculated in every individual by rearranging the equation

$$R_{\text{ac}} = 1/(1 - e^{-(\ln 2/t_{1/2,\text{app}}) \cdot \tau}),$$

where τ is the dosing interval (12 h).

Statistical procedures

Dose-normalized AUC within the single dose and multiple dose studies and across studies at the same dose was compared using the Peritz F -test procedure which includes adjustment for multiple comparisons [7].

Using the expectation maximization (EM) algorithm proposed by Racine-Poon [8] the population

mean and standard deviation of the pharmacokinetic model parameter estimates of greatest interest ($V_{\max}/F$, K_m , CL/F) were obtained from the individual subject parameter estimates after generating the covariance matrix with the full one- and two-compartment models.

Results

The drug was rapidly absorbed with no detectable delay for the initial absorption process ($t_{\text{lag}} = 0$). Two components to the absorption process were detectable after the first dose in one-third of the younger subjects in the single dose study (Figure 2) but in only one subject in the multiple dose study. They occurred more often at high than at low doses. The model suggested that in the 12 subjects where double peaks were seen the first drug input started immediately after dosing and explained 78% (range 50–96%) of the total dose administered. Maximum concentrations normalized to 100 mg ranged after single doses from 365 to 544 $\mu\text{g l}^{-1}$ (Table 1) and after the multiple dosing regimen from 585 to 789 $\mu\text{g l}^{-1}$.

The terminal portions of the plasma concentration-time profiles of the MAO-B inhibitor were characteristic of concentration-dependent elimination after single (Figure 2) and multiple dosing (Figure 3). In spite of this non-linearity in individual concentration-time profiles, $C_{\max}$ and AUC increased almost proportionally with the dose (Table 1). There was no significant difference in dose normalized $C_{\max}$ either in the single dose or in the multiple dose study (first and last doses). For the normalized AUC(0,12) and AUC(0,24) there was a slight trend to increase with increasing doses (Table 1). However, the only significant differences were detected in the multiple dose study (AUC(0,12) day 1: 100 mg vs 350 mg; day 10: 100 mg vs 250 and 350 mg). Steady-state plasma drug concentrations were achieved already on the third day of chronic dosing. The overall mean accumulation ratio last/first dose for $C_{\max}$ was 1.47 ± 0.36 (range 0.86–2.4) and for AUC(0,12) it was 1.61 ± 0.31 (range 0.97–2.2). No relevant difference was

Figure 2 Observed (●) and predicted (—; dual input/single elimination pathway model) plasma concentrations of lazabemide following a single dose of 250 mg to a young subject. The figure with log-lin scale illustrates the concentration-dependent elimination; on the lin-lin scale the dual input process is readily seen.

noted in any parameter after the first dose given to young and elderly volunteers.

Plasma drug concentrations in the single dose trial were described initially by a model allowing for only concentration-dependent elimination. Zero-order inputs were preferred over first-order processes to accommodate the rapid rise in concentrations after a dose. Irregularities around the peak could be modelled using two drug inputs, the second usually starting after a short lag time (Table 2). Although these models were well suited to describe drug concentrations after a single dose, they predicted a much higher accumulation of drug than was actually seen after multiple dosing. At a dosing level of 250 mg twice daily the AUC was expected to be four times higher after 7 days of dosing than after the first dose. The observed accumulation ratio was in most cases less than 2-fold. This discrepancy between prediction and observation was clearly due to model misspecification. Therefore, for the description of multiple dose data, the model was expanded to allow for a second, concentration-independent elimination clearance. Figures 3 and 4 show observed and predicted plasma drug concentrations for two subjects. Model parameters $V_{\max}/F$, K_m , CL/F and V_{ss}/F (Table 3) did not depend on the dose. The error model parameter V_0 was fixed at a negligibly small value (10^{-10}) and the PWR parameter at 2; the standard deviation scale factor was determined as $20 \pm 61 \mu\text{g l}^{-1}$. A one-compartment model was sufficient to describe the single dose data in young volunteers but for many of the elderly subjects (28 out of 37) a two-compartment

Figure 3 Observed (●) and predicted (—; single input/dual elimination pathway model) plasma concentrations of lazabemide following multiple doses of 200 mg twice daily to an elderly subject.

Figure 4 Comparison of plasma concentrations of lazabemide in a healthy elderly volunteer after first (day 1; ●) and last (day 10; ○) dose during a multiple dosing regimen of 350 mg twice daily.

Table 1 Dose-normalized maximum plasma concentrations and areas under plasma concentration-time curves of lazabemide after single and multiple dosing

<i>Parameter</i> ¹	<i>Dose (mg), administered every 12 h for multiple dosing</i>				
	100	150	200	220	300
<i>C</i> _{max} ($\mu\text{g l}^{-1}$) ²					
single dose	419 (91)	544 (216)	504 (79)	443 (63)	365 (42)
multiple dose					
first dose	469 (87)	480 (127)	509 (192)	—	477 (101)
last dose	585 (134)	673 (153)	789 (205)	—	739 (138)
(ratio last/first dose)	(1.25)	(1.40)	(1.55)	—	(1.55)
<i>AUC</i> (0,12) ($\mu\text{g l}^{-1} \text{h}$) ²					
multiple-dose					
first dose	3023 (505)	3046 (629)	3181 (450)	—	3597 (546)
last dose	4133 (819)	5266 (1402)	5695 (1464)	—	5974 ⁵ (1247)
(ratio last/first dose)	(1.37)	(1.73)	(1.79)	—	(1.66)
<i>AUC</i> (0,24) ($\mu\text{g l}^{-1} \text{h}$) ²					
single dose	—	3853 (738)	5338 (948)	4232 (1058)	3958 (403)
multiple dose					
first dose	4189 (680)	3832 (810)	4145 ³ (634)	—	4801 (1002)
last dose	5376 (1180)	7271 (1640)	7704 (2291)	—	7965 ⁵ (1648)
<i>t</i> _{max} (h) ⁶					
single dose	1.0 (0.50–2.0)	0.50 (0.48–4.0)	1.3 (1.0–2.0)	1.3 (1.0–4.0)	3.0 (2.0–6.0)
multiple dose					
first dose	1.5 (0.50–2.0)	1.0 (0.50–2.0)	1.0 (0.50–1.5)	—	2.0 (0.50–2.0)
last dose	0.50 (0.50–2.0)	1.5 (0.50–2.0)	1.0 (0.50–2.0)	—	1.3 (0.98–2.0)

¹Mean (s.d.).²Normalized to 100-mg dose.³Significantly different from corresponding value in single dose trial.⁴Significantly different from 150 mg dose.⁵Significantly different from 100 mg dose.⁶Median (range).

model was required to provide an adequate fit to the multiple dose data.

The combined mixed- and first-order elimination model predicted the observations after the first dose and the concentration profile after the last dose equally well in 37 out of 40 multiple dose data sets. However, trough concentrations during the accumulation phase tended in many cases to be lower than predicted. In three subjects concentrations after the last dose were systematically lower than expected (approximately 25%), based on the predictions after the first dose.

Discussion

A concentration-dependent elimination pathway for lazabemide was suggested by inspection of plasma drug concentration-time curves and supported by a single saturable elimination pathway model describing data following a single dose. The maximum elimination capacity estimated from the single pathway model (365 mg day^{-1}) predicted that oral doses greater than 360 mg day^{-1} would accumulate as long as drug was administered and did not reach steady state. However, plasma drug concentration-time curves obtained during the multiple dose study showed that accumulation was essentially complete and steady state was reached after less than 4 days even with daily doses up to 700 mg day^{-1} (Figure 3).

The failure of the single elimination pathway model to predict the behaviour after multiple doses pointed to the existence of an additional elimination process. Concentration-dependent elimination is well known in the commonly acceptable range of ethanol concentrations but the time course of elimination appears to be first-order at concentrations 10 times greater than that (reviewed by Holford [9]). The addition of a first-order elimination path in parallel with the concentration-dependent, mixed-order elimination process provided a good description of the time course of lazabemide not only after the first dose but also during accumulation to steady state and elimination of the last dose. First-order elimination dominates drug accumulation while the concentration-dependent process determines the drug concentration profile in the range of concentrations associated with major changes in MAO-B inhibition [10].

Renal clearance accounts for approximately 60% of clearance of unchanged drug in the dose range of 50–150 mg (unpublished results); metabolic clearance leads mainly to a single acidic metabolite formed by oxidative deamination of the side chain. The exact mechanism for the saturable elimination of the drug is not confirmed at present. However, the observations are compatible with deamination of the molecule by the MAO-B enzyme which is itself inhibited by lazabemide. After sufficiently large doses lazabemide's kinetics are principally determined by con-

Table 2 Single dose study: single elimination pathway parameter estimates¹

Parameter	Mean $\pm$ s.d.		Minimum	Maximum
	Two stage	EM		
$V_{\max}/F$ (mg h^{-1})	15.2 ± 5.9	14.9 ± 5.7	7.1	27.6
K_m ($\mu\text{g l}^{-1}$)	199 ± 135	187 ± 124	10	493
V_{ss}/F (l)	232 ± 39	—	155	332
T_{K01} (h)	0.62 ± 0.42	—	0.21	2.2
f_1 ²	0.93 ± 0.13	—	0.5	1
$t_{\text{lag}2}$ (h)	1.5 ± 1.5	—	0.25	5.7
T_{K02} (h)	1.6 ± 1.1	—	0.3	3.6

¹Estimates based on 35 data sets; 12 data sets required dual input model.

² f_1 in 12 data sets requiring dual input model: mean 78%, range 50–96%.

Table 3 Multiple dose study: dual elimination pathway parameter estimates¹

Parameter	Mean $\pm$ s.d.		Minimum	Maximum
	Two stage	EM		
$V_{\max}/F$ (mg h^{-1})	3.72 ± 2.24	2.83 ± 1.35	0.75	9.16
K_m ($\mu\text{g l}^{-1}$)	65 ± 58	36 ± 19	2.6	232
CL/F (l h^{-1})	15.3 ± 4.13	16.1 ± 3.8	6.9	23.6
V_{ss}/F (l)	229 ± 36	—	166	297
V_2/F (l)	92.8 ± 42	—	38.0	203
CL_{ic} (l h^{-1})	170 ± 172	—	—	—
T_{K0} (h)	0.90 ± 0.41	—	0.22	1.9

¹Estimates based on 37 data sets; 28 data sets required two-compartment disposition model.

centration-independent disposition processes. The observation of overall dose linearity in the key kinetic parameters $C_{\max}$ and AUC in the present studies suggests that the non-linear elimination pathway is only a small component of the overall disposition of the drug at doses of 200 to 400 mg day⁻¹. The ability to detect dose-dependent changes in dose normalized AUCs depends on the dose range studied. Predicted departures from linearity at the doses studied are of no clinical relevance. However, they are expected to become more important if doses much lower than 100 mg are studied.

Lazabemide was administered orally in both studies. Therefore, several of the model parameters determined are confounded by the extent of bioavailability. Although absolute bioavailability of the administered oral formulations is not known, almost complete extent of bioavailability of the drug is expected. After oral administration of radiolabelled compound over 95% of the dose was found in the urine (unpublished results), confirming almost complete uptake of drug from the gastrointestinal tract into the portal blood. Because 55% of an oral dose of 100 mg is eliminated unchanged in the urine, renal clearance of unchanged drug has been estimated to be 14.4 l h⁻¹ (unpublished results in healthy Japanese subjects). The numerical similarity of the previously found renal clearance and the first-order clearance found in our study (16.1 l h⁻¹) may be fortuitous, but it might also be suggestive of a mechanistic explanation. The saturable pathway would then be responsible for any first-pass metabolism after oral dosing. With a blood/plasma partition ratio of 1.2 (unpublished results), the blood K_m can be calculated to be around 43 µg l⁻¹. Assuming an hepatic blood flow of 90 l h⁻¹, average portal venous blood concentrations during absorption of 100 mg over 1 h would be around 1100 µg l⁻¹. The average intrinsic clearance by the mixed-order pathway during absorption would therefore be 2.5 l h⁻¹. From this value for total blood CL/F an hepatic extraction ratio of less than 3% is

expected [11]. It is realized that several assumptions are made in these calculations; based on present evidence these are not unreasonable.

The rate of absorption of lazabemide was very rapid without any detectable delay. However, in some cases not all of the drug was released at the same time from the formulations. In 12 subjects in the single dose trial double peaks were clearly seen. The fact that they were only seen when multiple tablets were given suggests that this reflects separation of tablets within the g.i. tract. The pharmacokinetic model developed needed to accommodate the irregularities in absorption profiles in order to provide a good description of observed concentrations at all times. This was achieved by allowing the dose to be absorbed by two sequential processes.

Based on the observed accumulation ratio of $C_{\max}$ and AUC(0,12) the apparent half-life of lazabemide determining accumulation is 7.5 ± 3.2 h and 8.8 ± 2.5 h, respectively. As expected this is somewhat shorter than the half-life (11 ± 3.9 h) predicted from the first-order clearance and V_{ss} .

The single and multiple dose studies reported were performed in two different populations of young and elderly healthy volunteers, both using very similar study protocols with respect to single dosing. When results across studies are compared the influence of age on the pharmacokinetics of lazabemide can be evaluated. From such a comparison it appears that no important changes occur in absorption or disposition parameters of lazabemide with progressing age in healthy people. The possibility exists that in the elderly more of a distribution phase is seen in the concentration-time profiles compared with young subjects.

The SAS code for the expectation maximization algorithm was kindly supplied by Dr A. Racine-Poon, Ciba-Geigy, Basel, Switzerland. Dr Ludger Banken, from F. Hoffmann-La Roche, gave valuable assistance in applying this code to our results.

References

- McDaniel KD. Clinical pharmacology of monoamine oxidase inhibitors. *Clin Neuropharmacol* 1986; **9**: 207–234.
- Fowler CJ. Selective inhibitors of monoamine oxidase types A and B and their clinical usefulness. *Drugs of the Future* 1982; **7**: 501–517.
- Da Prada M, Kettler R, Keller HH, Kyburz E, Burkard WP. Ro 19-6327: A novel highly selective and reversible MAO-B inhibitor. *Acta Pharmac Tox* 1987; **60** (Suppl): 10.
- Holford, NHG. *MKMODEL*. Biosoft, Cambridge, England, 1990.
- Fehlberg E. Low-order classical Runge-Kutta formulas including stepsize control and their applications to some heat transfer problems. *NASA Technical Report* 1969; R-315.
- Schwarz G. Estimating the dimension of a model. *Ann Stat* 1978; **6**: 461–464.
- Marcus R, Peritz E, Gabriel KR. On closed testing procedures with special reference to ordered analysis of variance. *Biometrika* 1976; **63**: 655–660.
- Racine-Poon A. A Bayesian approach to nonlinear random effects models. *Biometrics* 1985; **41**: 1015–1023.
- Holford NHG. Clinical pharmacokinetics of ethanol. *Clin Pharmacokin* 1987; **13**: 273–292.
- Holford NHG, Guentert TW, Dingemanse J, Kettler R. Pharmacodynamics of lazabemide, a reversible and selective inhibitor of monoamine oxidase B. *Br J clin Pharmac* 1994; **37**: 553–557.
- Wilkinson GR, Shand DG. A physiological approach to hepatic drug clearance. *Clin Pharmac Ther* 1975; **18**: 377–390.

(Received 14 October 1993,
accepted 31 January 1994)