Clinical and pharmacokinetic results with a new ultrashort-acting calcium antagonist, clevidipine, following gradually increasing intravenous doses to healthy volunteers

H. Ericsson, C. Fakt, Å. Jolin-Mellgård, M. Nordlander, L. Sohtell, M. Sunzel & C. G. Regårdh

Astra Hässle Research Laboratories, Astra Hässle AB, S-431 86 Mölndal, Sweden

Aims To investigate the tolerability and safety of clevidipine in healthy male volunteers during intravenous infusion at gradually increasing dose rates and to obtain preliminary information on the pharmacokinetics and pharmacodynamic effects of the drug.

Methods Twenty-five subjects were enrolled in the study and twenty-one of them were included twice, resulting in a total of forty-six study entries encompassing 20 min infusions of clevidipine at target dose rates ranging from 0.12 to 48 nmol min⁻¹ kg⁻¹. Haemodynamic variables and adverse events were recorded throughout the study. Concentrations of clevidipine and its primary metabolite, H 152/81, were followed in whole blood, and the pharmacokinetics were evaluated by non-compartmental and compartmental analysis. An E_{max} model was fitted to the effect on mean arterial pressure (MAP) over heart rate (HR) and the corresponding blood concentrations of clevidipine.

Results Clevidipine was administered up to a target dose rate of 48 nmol min⁻¹ kg⁻¹, where a pre-determined escape criterion was reached (HR > 120 beats min⁻¹) and the study was stopped. The most common adverse events were flush and headache, which can be directly related to the mechanism of action of clevidipine. There was a linear relationship between blood concentration and dose rate in the range studied. The median clearance value determined by non-compartmental analysis was 0.125 l min⁻¹ kg⁻¹. Applying the population approach to the sparse data on clevidipine concentrations, an open two compartment pharmacokinetic model was found to be the best model in describing the disposition of the drug. The population mean clearance value determined by this method was 0.121 l min⁻¹ kg⁻¹, and the volume of distribution at steady state was 0.56 l kg⁻¹. The initial half-life, contributing by more than 80% to the total area under the blood concentration-time curve following i.v. bolus administration, was 1.8 min, and the terminal half-life was 9.5 min. At the highest dose rates, MAP was reduced by approximately 10%, and the HR reached the pre-determined escape criterion for this study (> 120 beats min⁻¹).

Conclusions Clevidipine is well tolerated and safe in healthy volunteers at dose rates up to at least 48 nmol min⁻¹ kg⁻¹. The pharmacokinetics are linear over a wide dose range. Clevidipine is a high clearance drug with extremely short half-lives. The effect of clevidipine on the blood pressure was marginal, probably due to a compensatory baroreflex activation in this population of healthy volunteers. A simple E_{max} model adequately describes the relationship between the pharmacodynamic response (MAP/HR) and the blood concentrations of clevidipine.

Keywords: clevidipine, ultrashort-acting, calcium antagonist, pharmacokinetics, population pharmacokinetics, blood-pressure reduction, cardiac surgery

Introduction

A limited number of drugs are available today for the reduction and control of blood pressure in connection

with cardiac surgical procedures. To be able to control blood pressure properly during and following surgery, suitable drugs are expected to have a rapid onset and offset of action. The most common blood pressure reducing regimens used perioperatively today are intensified anaesthesia and/or administration of non-selective vasodilators [1], e.g. glyceryltrinitrate (GTN) and sodium

Correspondence: Dr H. Ericsson, Pharmacokinetic and Drug Metabolism, Astra Hässle AB, S-431 83 Mölndal, Sweden.

Received 23 March 1998, accepted 15 January 1999.

Twenty-five healthy male Caucasians (age 29 ± 5 years; weight 75 ± 6 kg, height 179 ± 5 cm) were enrolled in the study, twenty-one of whom were included twice, giving a total of forty-six study entries. All subjects were given verbal and written information about the study. Signed and witnessed written informed consent was obtained from all subjects before enrolment. All subjects participating in the study were medically examined within 14 days prior to the first study day. Demographics and medical histories were recorded. A general physical

Frequent blood samples (approximately 1.5 ml) were drawn from an indwelling plastic cannula in a forearm vein from the arm contralateral to the arm utilised for drug infusion. The blood was rapidly transferred to pre-weighed test tubes containing 1.5 ml sodium dodecyl sulphate solution (SDS solution) and 150 μ l ascorbic acid solution which on being mixed immediately stopped the hydrolysis and prevented oxidation of the primary

metabolite, H 152/81. The samples were then weighed, frozen (within 1 h) and stored at -70°C until analysis.

Analytical methods

The blood concentrations of clevidipine were analysed by a method based on gas chromatography-mass-spectrometry, while the content of the primary metabolite H 152/81 was analysed by liquid chromatography [8]. The limit of quantitation (LOQ) was 5 nmol l^{-1} for clevidipine and 50 nmol l^{-1} for the metabolite. The intra-day coefficients of variation (CV) of blood standards for clevidipine ranged between 0.7 and 11.4% and between 1.4–4.0% for the metabolite.

Pharmacokinetic non-compartmental analysis

The blood clearance of clevidipine (CL_b) was calculated for each individual infusion as $\text{CL}_b = R_{\text{inf}}/C_{\text{ss}}$; where R_{inf} was the infusion rate and C_{ss} was the median blood concentration obtained during the last 10 min of clevidipine infusion.

A non-compartment model (WinNonlin®, ver. 1.1, Scientific consulting Inc., Apex, NC, U.S.) was used to determine the pharmacokinetics of the primary metabolite. The maximum concentration, C_{max} , was determined as the highest observed concentration, and t_{max} was the time to reach this concentration. The total area under the blood concentration *vs* time curve (AUC) was calculated by the linear and log-linear trapezoidal rule from time zero to the last observation ($\text{AUC}(0, x) + C_t/\lambda_Z$, where C_t was the predicted concentration at the last observed time point. The terminal rate constant, λ_Z , was calculated by linear regression analysis of $\ln$ blood concentration *vs* time, using the last blood concentrations from each subject. The elimination half-life was calculated as $\ln 2/\lambda_Z$.

The blood clearance for the metabolite (CL_{met}) was calculated as $\text{CL}_{\text{met}} = \text{Dose}/\text{AUC}$. The volume associated with the terminal phase (V_Z) was calculated as: $V_Z = \text{Dose}/(\text{AUC} \cdot \lambda_Z)$.

Since *in vitro* studies in human whole blood have shown that clevidipine is quantitatively metabolised to its corresponding primary metabolite, it was anticipated that the same reaction would occur in the *in vivo* situation [9]. Accordingly, the dose of the metabolite was assumed to be equal to the clevidipine dose.

Pharmacokinetic compartmental analysis

Due to the study design and the extremely rapid post-infusion decline in clevidipine concentrations, it was not possible to perform individual compartmental analysis, since the data were too sparse. Instead, the pharmaco-

kinetic parameters of clevidipine were determined by non-linear mixed effect modelling using the software program P-PHARM® (ver. 1.4, SIMED, Creteil, France). The time course of clevidipine concentration was described by monoexponential or biexponential disposition functions. The two models were compared using the Akaike Information Criterion (AIC) [10] and inspection of the residuals. A heteroscedastic ($1/C_{\text{pred}}$) distribution of error was used in all analyses. The blood clearance (CL_b), initial volume of distribution (V_1) and the rate constants for drug transfer between the central and the peripheral compartments (k_{12} and k_{21}) were obtained directly from the fitting function and were assumed to be log-normally distributed. Thus, the population mean and an estimate of its variability was obtained for these parameters. The rest of the reported pharmacokinetic parameters were calculated from the estimated population mean values using standard pharmacokinetic equations [11]. In addition, the individual pharmacokinetic parameters were obtained from a maximum *a posteriori* probability (MAP) Bayesian fitting procedure [12].

The fractional area under the curve for the initial phase was calculated as: $(C_1/\lambda_1)/(C_1/\lambda_1 + C_2/\lambda_Z)$ where C_1 and C_2 represent the fractional zero time intercepts of the initial and terminal phase, respectively, after a unit i.v. bolus.

The pharmacokinetic analysis (non-compartmental and compartmental) of clevidipine and the primary metabolite were estimated at dose levels that resulted in blood concentrations which could be determined with sufficient precision and accuracy. Thus, the clevidipine parameters were determined from subjects receiving dose rates from 1.5 to $48\text{ nmol min}^{-1}\text{ kg}^{-1}$, while the corresponding dose rates for the primary metabolite were 6 to $48\text{ nmol min}^{-1}\text{ kg}^{-1}$.

Pharmacodynamic evaluation

The mean percentage change in MAP, systolic blood pressure (SBP), diastolic blood pressure (DPB) and HR from baseline values was calculated for each dose rate from $3\text{ nmol min}^{-1}\text{ kg}^{-1}$ and upwards. MAP was calculated as: $\text{MAP} = [(\text{SPB} - \text{DBP})/3] + \text{DBP}$.

Pharmacodynamic and pharmacokinetic evaluation

As blood pressure reduction in healthy volunteers is counteracted by a compensatory increase in heart rate, the ratio MAP/HR was used as an indirect measure of systemic vascular resistance (SVR) and assumed to be the best predictor of the primary pharmacological effect induced by clevidipine. This ratio was used to evaluate the relationship between the effect and the blood

Figure 2 The venous blood concentrations of clevidipine (a) and the primary metabolite (b) *vs* time in four different individuals after a target dose rate of $36 \text{ nmol min}^{-1} \text{ kg}^{-1}$ during 20 min infusion of clevidipine.

concentration of clevidipine. A simple E_{max} -model, ($\text{Effect} = E_{\text{max}} \times C / (EC_{50} + C)$), where E_{max} is the maximum effect and EC_{50} is the concentration at the half maximum effect, was fitted to the pooled data by the computer program WinNonlin[®]. Recordings of the percentage reduction in MAP/HR from pre-dose values during clevidipine infusion and the corresponding blood concentrations were used in the analysis.

Results

Clevidipine was well tolerated up to a target dose rate of $48 \text{ nmol min}^{-1} \text{ kg}^{-1}$. At this dose rate, heart rate increased above $120 \text{ beats min}^{-1}$ in a separate recording in more than 50% of the subjects, and the study was stopped.

Adverse events

The most common AEs were flush (40%) and headache (20%). Both of them were reported to be mild or moderate. The AEs were more frequent at the higher dose rates. These adverse events occurred during clevidipine infusion and disappeared shortly after the infusion was terminated. No serious adverse event was reported in the study.

Pharmacokinetics of clevidipine

The individual blood concentrations of clevidipine *vs* time after a target dose rate of $36 \text{ nmol min}^{-1} \text{ kg}^{-1}$ are shown in Figure 2a. The mean, median and range of blood clearance obtained from the non-compartmental analysis are given in Table 1. The median blood clearance was $0.125 \text{ l min}^{-1} \text{ kg}^{-1}$ with a range between 0.092 and $0.276 \text{ l min}^{-1} \text{ kg}^{-1}$. Blood clearance was not affected by the dose rate in the range 1.5 to $48 \text{ nmol min}^{-1} \text{ kg}^{-1}$. Consequently, there was a directly proportional increase in the steady state blood levels in relation to the dose rate.

An open two-compartment model was the best model to describe the blood concentration *vs* time course of clevidipine. The AIC value decreased from 4.21 to 4.12 when using a two-compartment model instead of a monoexponential disposition function, and the visual inspection of the residual plots also favoured the two compartment model. The estimated population mean and the derived pharmacokinetic parameters are given in Table 1. The blood clearance obtained from this analysis was $0.121 \text{ l min}^{-1} \text{ kg}^{-1}$. The volume of the distribution

Table 1 The pharmacokinetics of clevidipine determined from venous blood concentrations during and following termination of the clevidipine infusion.

	$CL^a)$ ($\text{l min}^{-1} \text{ kg}^{-1}$)	$CL^b)$ ($\text{l min}^{-1} \text{ kg}^{-1}$)	$CL^c)$ ($\text{l min}^{-1} \text{ kg}^{-1}$)	$V_1^c)$ (l kg^{-1})	$V_{ss}^d)$ (l kg^{-1})	$t_{1/2, \alpha_1}^d)$ (min)	$t_{1/2, \beta}^d)$ (min)	$C_1^d)$ (%)	$C_2^d)$ (%)	$AUC_{0-\infty}^d)$ (%)
Mean	0.146	0.122	0.121	0.36	0.56	1.8	9.5	95.9	4.1	81.6
Median	0.125	0.118								
Min	0.090	0.094								
Max	0.276	0.158								

^{a)}Individual non-compartmental analysis. ^{b)}Bayesian estimate. ^{c)}Population mean. ^{d)}Derived from the population mean values (CL , V_1 , k_{12} and k_{21}).

Figure 3 The population fit (thick line) and the posterior individual fit (thin lines) of a two-compartment model to the data, normalized to a dose rate of $12 \text{ nmol min}^{-1} \text{ kg}^{-1}$ (a) and the observed blood concentrations of clevidipine *vs* the predicted mean population concentrations (b).

at steady state (V_{ss}) was 0.56 l kg^{-1} , and the half-life of the initial ($t_{1/2,\lambda_1}$) and the terminal phase ($t_{1/2,Z}$) was 1.8 and 9.5 min, respectively. The mean population fit and the posterior individual fit of a two-compartment model to the data are shown in Figure 3a, the data are normalized to a dose rate of $12 \text{ nmol min}^{-1} \text{ kg}^{-1}$. The observed blood concentrations of clevidipine *vs* the predicted mean population concentrations are shown in Figure 3b. The median blood clearance value obtained from the Bayesian

estimate was $0.118 \text{ l min}^{-1} \text{ kg}^{-1}$, with a range between 0.094 and $0.158 \text{ l min}^{-1} \text{ kg}^{-1}$.

By using the model estimated population mean and the derived pharmacokinetic parameters it can be calculated that more than 80% of the total AUC is associated with the initial phase of the blood concentration *vs* time curve if the drug is given as an i.v. bolus administration.

Pharmacokinetics of primary metabolite

The individual blood concentrations of the primary metabolite H 152/81 *vs* time after a target dose rate of $36 \text{ nmol min}^{-1} \text{ kg}^{-1}$ of clevidipine are shown in Figure 2b. The mean pharmacokinetic parameters of the metabolite, calculated from each dose rate of clevidipine, are given in Table 2. The mean clearance of the metabolite was $0.034 \text{ l h}^{-1} \text{ kg}^{-1}$. The volume of the terminal phase (V_Z) was 0.38 l kg^{-1} , and the mean terminal phase ($t_{1/2,Z}$) was approximately 8 h. The maximal concentration of the metabolite, C_{max} , was $1.1 \mu\text{mol l}^{-1}$ (the data are normalised to a dose rate of $12 \text{ nmol min}^{-1} \text{ kg}^{-1}$) and was reached, t_{max} , within 5 min of terminating the clevidipine infusion.

Pharmacodynamics and effect-concentration relationship

The mean effect on MAP and HR, expressed as percentage change from pre-dose values, obtained during the last 10 min of the clevidipine infusion at different dose rates, is shown in Figure 4. The corresponding values of SBP and DBP are shown in Figure 5. The individual values of the percentage change in MAP/HR from baseline, obtained during the last 10 min of the clevidipine infusion, *vs* the blood concentration of clevidipine at the time of effect recording are shown in Figure 6. The solid line represents the fit of the E_{max} -model to the pooled data. According to the model, the maximum reduction in MAP/HR (E_{max}) was 45.4%, and the concentration at half maximum effect (EC_{50}) was 12.1 nmol l^{-1} . The statistical criteria, Akaike and Schwartz criteria, did not favour any more complex sigmoidal E_{max} -model.

Table 2 The pharmacokinetic parameters of the primary metabolite H 152/81 determined after administration of clevidipine at different dose rates.

	CL_{met} ($\text{l h}^{-1} \text{ kg}^{-1}$)	C_{max}^a (nmol l^{-1})	t_{max} (min)	$t_{1/2,Z}$ (h)	V_Z (l kg^{-1})
Mean	0.034	1116	24.9	8.1	0.38
s.d.	0.007	132	2.8	1.7	0.08
Median	0.032	1079	25.0	8.0	0.36
Min	0.025	928	20.3	5.8	0.29
Max	0.049	1416	30.0	12.0	0.60

^aThe values are normalized to a dose rate of $12 \text{ nmol min}^{-1} \text{ kg}^{-1}$.

Figure 4 The mean $\pm$ s.d. effect on MAP ($\blacksquare$, mean basal value = 83 mmHg) and HR ($\square$, mean basal value = 55 beats min^{-1}) at steady state during clevidipine infusion at different dose rates. $n = 4$, $\star n = 3$.

Figure 5 The mean $\pm$ s.d. effect on SBP ($\blacksquare$, mean basal value = 109 mmHg) and DBP ($\square$, mean basal value = 71 mmHg) at steady state during clevidipine infusion at different dose rates. $n = 4$, $\star n = 3$.

Discussion

Clevidipine is a vascular selective calcium antagonist [13]. As such, it reduces arterial blood pressure by decreasing systolic vascular resistance due to arteriolar dilatation [14]. In the present study in young healthy male volunteers, clevidipine was safe and well-tolerated at the dose rates studied; 0.12–48 $\text{nmol min}^{-1} \text{kg}^{-1}$. At the highest dose rate (baseline mean MAP = 82 mmHg and mean baseline HR = 64 beats min^{-1}), one of the predetermined safety endpoints (HR > 120 beats min^{-1}) was exceeded in individual recordings in two subjects and the study was stopped. The most common AEs in the present study were flush and headache, which can be directly related to the mechanism of action of clevidipine. These AEs are also common during treatment with other dihydropyridine calcium antagonists [15].

Figure 6 The individual values of MAP/HR vs the blood concentrations of clevidipine. The solid line represents the model-derived relationship between the blood concentration and effect.

There was a linear relationship between the dose rate and blood concentration of clevidipine at steady state over the entire dose range. The median blood clearance value obtained from the non-compartmental analysis and the population mean were virtually identical. However, a comparison of the mean values from the individual non-compartmental analysis and the population mean shows that the clearance value obtained from the non-compartmental is approximately 20% higher than the corresponding mean values from the population estimates. The reason for this discrepancy is that the non-compartmental analysis is based on only a few blood concentrations from each individual. In a few individuals the clearance was affected by outlying concentrations resulting in an increased average clearance.

Because clevidipine undergoes extensive extravascular metabolism [16], the use of a two-compartment model with elimination from the central compartment might be incorrect. We cannot exclude hydrolysis in the tissues from the peripheral compartment. However, irrespective of the model chosen, the estimate of the clearance value will not be affected since it is derived from the ratio between dose and AUC [17]. The blood clearance was extremely high, exceeding the liver blood flow and cardiac output, while the volume of distribution at steady state was relatively small. The high clearance value and the small volume of distribution result in extremely short half-lives of clevidipine, 1.8 and 9.5 min, respectively. Due to the rapid decline in blood concentrations following termination of the clevidipine infusion, the terminal half-life is rather uncertain, as there was only time for a few observations before the limit of quantification was reached. However, the present study indicated

a terminal half-life of approximately 10 min. A more precise study of the terminal phase(s) would require larger doses or development of a more sensitive assay and more frequent and extended blood sampling than in the present study. However, the slow phase(s) will have a negligible influence on the time to reach steady state and on the post-infusion curve following various infusion times, since most of the post-infusion decline is associated with the initial rapid decline. For clevidipine, the AUC associated with the short half-life covers more than 80% of the total area under the curve, following an i.v. bolus.

The relevance of the terminal half-life of rapidly eliminated drugs intended to be used during anaesthesia has been discussed in the literature. It has been emphasized that a comparison of the terminal half-lives of different drugs is misleading, since it does not take into account the overall decay of the blood/plasma concentration *vs* time curve [18–20]. To circumvent the rather confusing use of different half-lives of bi- or multiphasically declining drug concentrations, Hughes *et al.* [21] have suggested the use of 'context-sensitive half-time' to describe the time for the post-infusion blood levels to decrease by 50% after stopping the infusion, where context refers to the duration of the infusion. According to this definition, the context-sensitive half-times for clevidipine will be virtually identical to the initial half-life of clevidipine, irrespective of the duration of the infusion as the 50% decline appears to be covered by the initial phase of the post-infusion curve even after infusion times exceeding four terminal half-lives, i.e., when this phase no longer affects the time course of the blood levels of clevidipine.

The derived pharmacokinetic parameters for the primary metabolite were very different from the pharmacokinetics of the parent compound. The metabolite is a low clearance compound with a small volume of distribution. The terminal half-life was approximately 8 h, which is in agreement with previously reported half-lives in healthy Japanese subjects treated with felodipine [22]. The $t_{\max}$ for the metabolite was reached within minutes following termination of the clevidipine infusion, indicating that the rapid post-infusion decline in clevidipine concentration is due to elimination of the compound rather than distribution, (Table 2 and Figure 2b). The effect on MAP was back to pre-dose levels 10 min after termination of the clevidipine infusion for all doses whereas the effect on MAP/HR was virtually back to pre-dose levels within 5 min after termination of the clevidipine infusion for dose rates up to $12 \text{ nmol min}^{-1} \text{ kg}^{-1}$. This is in agreement with the results obtained following a 1h infusion of clevidipine to healthy volunteers ($12 \text{ nmol min}^{-1} \text{ kg}^{-1}$) where the effect on MAP and HR was back to pre-dose values 15 min after discontinuation of the infusion [16]. This rapid recovery of effect is consistent with the initial rapid

half-life of clevidipine and negligible pharmacological effect of the primary metabolite.

During ongoing infusion at the three highest dose rates, small effects on DBP, SBP and MAP were observed, while the heart rate increased from a mean baseline value of 54 ± 9 to $86 \pm 10 \text{ beats min}^{-1}$. These findings are in agreement with those for other dihydropyridine calcium antagonist when given to healthy volunteers in which the heart rate increases due to a compensatory baroreflex activation [23]. However, clevidipine will be used during general anaesthesia and during this condition the baroreflex sensitivity is decreased [24]. Therefore, no compensatory heart rate increase was observed when clevidipine was administered to post-cardiac surgical patients during anaesthesia despite a blood pressure reduction of about 20% [14]. Probably due to the baroreflex activation in the normotensive subjects studied the changes in the blood pressure were small [25], allowing no evaluation of a potential relationship between clevidipine blood levels and the effect on blood pressure. On the other hand the effect on SVR, the primary physiological effect of clevidipine, was evaluated by the ratio MAP/HR, an indirect measure of SVR assuming constant stroke volume. A simple $E_{\max}$ -model adequately described the relationship between this ratio and the blood concentration of the drug. The EC_{50} was approximately 12 nmol l^{-1} , a steady state blood concentration resulting from a dose rate of approximately $1.5 \text{ nmol min}^{-1} \text{ kg}^{-1}$.

In conclusion, clevidipine is well-tolerated and safe in the dose range studied and no infusion was stopped due to an adverse event. The most common adverse events are flush and headache. The pharmacokinetics derived from the present study show that clevidipine is a high clearance drug with an ultrashort-acting profile in healthy volunteers. The clearance value indicates metabolism by esterases in the blood and extravascular tissues. The time to reach steady state is short, and the results obtained indicate that the initial post-infusion phase curve may reflect both the distribution and elimination of the drug, whereas the terminal phase might reflect redistribution of the drug from extravascular tissues into the systemic circulation. Clevidipine causes only a small blood pressure reduction in healthy volunteers, probably due to a pronounced compensatory baroreflex activation. A simple $E_{\max}$ model describes the relationship between the pharmacodynamic response (MAP/HR) and the blood concentration of clevidipine.

References

- 1 Vuylsteke A, Feneck R, Latimer R, *et al.* Type of perioperative treatment delays extubation and prolongs ICU stay in cardiac surgery. *Br J Anaesth* 1996; **76**: A30.
- 2 Kaplan JA, Finlayson DC, Woodward S. Vasodilator therapy

- after cardiac surgery: a review of the efficacy and toxicity of nitroglycerin and nitroprusside. *Can Anaesth Soc J* 1980; **3**: 254–259.
- 3 Friederich JA, Butterworth JF. Sodium nitroprusside: twenty years and counting. *Anesth Analg* 1995; **81**: 152–162.
 - 4 Mason DT, Braunwald E. The effect of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm. *Circulation* 1965; **32**: 755.
 - 5 Zäll S, Kirnö K, Milocco I, Ricksten S-E. Vasodilation with adenosine or sodium nitroprusside after coronary artery bypass surgery. A comparative study on myocardial blood flow and metabolism. *Anesth Analg* 1993; **76**: 493–497.
 - 6 Lawrence C J, Lestrade A, De Lange S. Comparative study of isradipine and sodium nitroprusside in the control of hypertension in patients following coronary artery-bypass surgery. *Acta Anaesthesiol Scand suppl* 1993; **37**: 48–52.
 - 7 Cook E, Clifton GG, Vargas R, et al. Pharmacokinetics, pharmacodynamics, and minimum effective clinical dose of intravenous nicardipine. *Clin Pharmacol Ther* 1990; **47**: 706–718.
 - 8 Fakt C, Stenhoff H. Determination of an ultrashort-acting antihypertensive dihydropyridine in blood using capillary gas chromatography mass spectrometry and of the primary metabolite using liquid chromatography and fluorescence detection. *J Chromatogr B Biomed. appl.* (in press).
 - 9 Ericsson H, Tholander B, Regårdh CG. *In vitro* hydrolysis rate and protein binding of clevidipine, a new ultrashort-acting calcium antagonist metabolised by esterases, in different animal species and man. *Eur J Pharm Sci* (in press).
 - 10 Yamaoka K, Nakagawa T, Uno T. Application of Akaike's information criteria (AIC) in the evaluation of linear pharmacokinetic equations. *J Pharmacokinetic Biopharm* 1976; **6**: 165–175.
 - 11 Wagner J. Linear pharmacokinetic equation allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. *J Pharmacokinetic Biopharm* 1976; **4**: 443–467.
 - 12 PPHARM user's guide. 2nd ed. SIMED, Creteil, France 1994.
 - 13 Levy JH, Huraux C, Nordlander M. Treatment of perioperative hypertension. In *Calcium antagonists in clinical medicine*, ed Epstein M. Philadelphia: Hanely and Belfus, 1997: 345–358.
 - 14 Kieler-Jensen N, Jolin-Mellgård Å, Nordlander M, Ricksten SE. Myocardial circulatory and metabolic effects of clevidipine after coronary artery bypass grafting (CABG) *Br J Anaesth* 1997; **78**: A12.
 - 15 Elvelin L, Kennerfalk A, Elmfeldt D. Tolerability and safety of felodipine. *Cardiovasc Drug Rev* 1993; **11**: 126–147.
 - 16 Ericsson H, Fakt C, Höglund L, et al. Pharmacokinetics and pharmacodynamics of clevidipine in healthy volunteers after intravenous infusion. *Eur J Clin Pharmacol* (in press).
 - 17 Benett LZ. General treatment of linear mammillary models with elimination from any compartment used in pharmacokinetics. *J Pharm Sci* 1972; **61**: 536–541.
 - 18 Egan T, Lemmens H, Fiset P, et al. The pharmacokinetics of the new short-acting opioid remifentanyl (GI87084B) in healthy adult male volunteers. *Anesthesiology* 1993; **79**: 881–892.
 - 19 Parivar K, Wessen A, Widman M, Nilsson A. Pharmacokinetics of etanalone following bolus and constant rate infusion. *J Pharmacokinetic Biopharm* 1997; **24**: 535–549.
 - 20 Shafer S, Varvel J. Pharmacodynamics, and rational opioid selection. *Anesthesiology* 1991; **74**: 53–63.
 - 21 Hughes M, Glass P, Jacobs J. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology* 1992; **76**: 334–341.
 - 22 Ohtake Y, Sakamoto T, Nishioka R, Uno K, Tabata S. Metabolic fate of felodipine in man. In search of new dihydropyridine metabolites. *Drug Invest* 1992; **4**: 528–534.
 - 23 Soons PA, Cohen AF, Breimer DD. Comparative effects of felodipine, nitrendipine and nifedipine in healthy subjects: concentration-effect relationships of racemic drugs and enantiomers. *Eur J Clin Pharmacol* 1993; **44**: 113–120.
 - 24 Tanaka M, Nishikawa T. Arterial baroreflex function in humans anesthetized with sevoflurane. *Anesthesiology* 1997; **87**: A132.
 - 25 Folkow B, Neil E. In *Circulation*, New York, London, Toronto: Oxford University Press, 1971.