

Pharmacokinetics and Arteriovenous Differences in Clevidipine Concentration following a Short- and a Long-term Intravenous Infusion in Healthy Volunteers

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Background: Clevidipine is an ultra-short-acting calcium antagonist developed for reduction and control of blood pressure during cardiac surgery. The objectives of the current study were to determine the pharmacokinetics of clevidipine after 20-min and 24-h intravenous infusions, and to determine the relation between the arterial and venous concentrations and the hemodynamic responses to clevidipine in healthy volunteers.

Methods: Four volunteers received clevidipine for 20 min, and eight subjects were administered clevidipine intravenously for 24 h at two different dose rates. Arterial and venous blood samples were drawn for pharmacokinetic evaluation, and blood pressure and heart rate were recorded.

Results: A triexponential disposition model described the pharmacokinetics of clevidipine. The mean arterial blood clearance of clevidipine was $0.069 \text{ l} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and the mean volume of distribution at steady state was 0.19 l/kg . The duration of the infusion had negligible effect on the pharmacokinetic parameters, and the context-sensitive half-time for clevidipine, simulated from the mean pharmacokinetic parameters derived after 24 h infusion at the highest dose, was less than 1 min. The arterial blood levels reached steady state within 2 min of the start of infusion and were about twice as high as those in the venous blood at steady state. The peak response preceded the peak venous concentration and was slightly delayed from the peak arterial blood concentration.

Conclusion: Clevidipine is a high clearance drug with a small volume of distribution, resulting in extremely short half-lives in healthy subjects. The initial rapid increase in the arterial blood concentrations and the short equilibrium time between the blood and the biophase suggest that clevidipine can be rapidly titrated to the desired effect. (Key words: Arteriovenous; context-sensitive times; decrement times.)

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THE therapeutic agents available today for reduction and control of blood pressure in connection with cardiac surgery are few. A rapid onset and recovery from effect is needed to be able to control blood pressure properly. Common treatments used today aim to intensify the anesthesia or administer a nonselective vasodilator, such as nitroglycerin or sodium nitroprusside,¹ each of which has a pharmacokinetic profile that allows rapid titration to the desired effect. Calcium antagonists are also used, their hemodynamic profile has been claimed to be ideal for cardiac surgery.^{1,2} However, among the calcium antagonists available today there is none whose pharmacokinetic profile allows a minute-to-minute titration to the desired effect.^{3,4}

Clevidipine (fig. 1) is a new ultra-short-acting, vascular selective calcium antagonist undergoing clinical trials for evaluation of its suitability for reducing and controlling blood pressure during cardiac surgery.⁵ The compound is structurally related to felodipine, another calcium antagonist of the dihydropyridine type, but clevidipine contains an ester linkage, which results in rapid and extensive metabolism in extravascular tissues and blood to the corresponding inactive carboxylic acid (fig. 1).^{6,7}

Studies on other short-acting ester-containing compounds, such as esmolol, atracurium, and remifentanyl, have demonstrated marked arteriovenous concentration differences.⁸⁻¹⁰ Initial clinical studies with clevidipine have also indicated an arteriovenous difference in the blood concentrations.^{7,11} In addition, a lag time of 0.5-1.0 min between the end of the infusion and the start of the rapid decay of venous blood concentrations has been observed.⁷

The primary objective of this study was to compare the pharmacokinetics of clevidipine if given as a short-term (20-min) or a long-term (24-h) intravenous infusion of therapeutically relevant doses in healthy volunteers. Furthermore, the relation between arterial and venous blood concentration and the hemodynamic response was studied after the short clevidipine infusion.

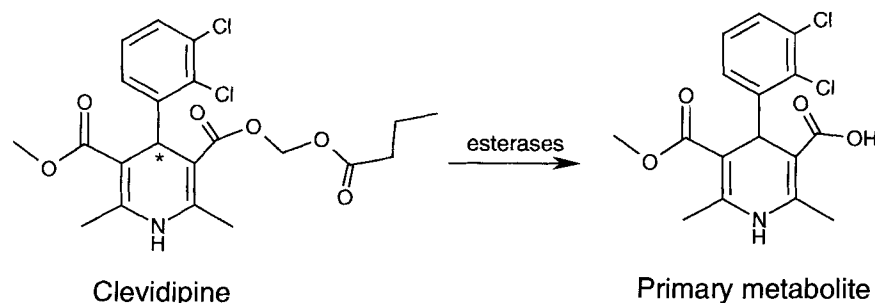


Fig. 1. The chemical structure of clevidipine and the primary metabolite. Asterix = the chiral center of clevidipine.

Methods

Subjects and Study Design

This open single-dose study was approved by the Ethics Committee of the University of Gothenburg, Sweden. Fifteen healthy male Caucasians (age 28.3 ± 4.7 yr, range 23–38 yr; weight 77.8 ± 6.0 kg, range 66–86 kg) were randomized to the study. The following inclusion criteria were used: no significantly abnormal physical findings, including electrocardiogram, or laboratory values outside the normal range at the pretreatment physical examination; systolic blood pressure less than 140 mmHg and diastolic blood pressure less than 85 mmHg; males 20–40 yr of age; body weight 66–86 kg; body mass index (weight/height squared) 19–27 kg/m²; and signed informed consent to participation in the study. The following exclusion criteria were used: significant clinical illness or prescribed medicine within 2 weeks or blood donation within 12 weeks preceding the first study day; requirement of concurrent medication; and history of cardiac, renal, hepatic or significant gastrointestinal disease, vascular headache, migraine, or alcohol or drug abuse.

All subjects participating in the study were medically examined within 14 days before the start of the study. Each subject's medical history was recorded. A general physical examination including measurement of blood pressure and heart rate and a 12-lead electrocardiogram was performed. A physical examination was also performed at the follow-up visit 2–5 days after drug infusion.

Dose Administration

Twelve healthy male volunteers received intravenous infusions of clevidipine over periods of either 20 min or 24 h. The subjects were randomly assigned to three groups. Four subjects received a 20-min infusion of clevidipine at a dose rate of $7 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; the short-infusion group. The remaining eight subjects were

administered clevidipine for 24 h at a final dose rate of either $2 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, the low-infusion group, or $7 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, the high-infusion group. In the low-infusion group, the infusion rate was escalated from an initial rate of $0.5 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to $4.0 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, with increments of $0.5 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and infusion periods of 15 min for each step. After 120 min the infusion rate was decreased to $2 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and kept constant until the end of the infusion. In the high-infusion group, the infusion rate was escalated from 0.5 to $7.0 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, the increment was $0.5 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and each infusion lasted for 10 min. The final infusion rate was kept constant for a total infusion time of 24 h.

Clevidipine was formulated in a 20% lipid emulsion (Intralipid; Pharmacia and Upjohn, Stockholm, Sweden) and the concentrations of clevidipine were 0.3 or 1.0 mg/ml.

The subjects were instructed to have dinner no later than 7 P.M. and abstain from all food and fluid intake after 10 P.M. the evening before the study day. Standardized meals were served at predetermined time points after the start of the infusion. No use of alcohol or over-the-counter drugs was permitted for 2 days before the study day. No subject took prescription drugs in the 2 weeks before the study. Tobacco and nicotine in any form were not allowed during the study day or during the fasting period preceding drug infusion.

Pharmacodynamic Measurements

Blood pressure and heart rate were planned to be continuously recorded with a Finapres cuff (Boc Ohmeda 2300, Louisville, CO) during the dose escalation and during cessation of the 24-h infusion. Additional heart rate and blood pressure measurements were made with a sphygmomanometer during the 24-h infusion experiment and up to 8 h after cessation of the infusion.

Blood Sample Collection and Analysis

During and after the end of the clevidipine infusion, frequent blood samples for determination of clevidipine were drawn from cannulas placed in a forearm vein and in the radial artery. Venous blood samples were collected at each dose rate during dose escalation, whereas arterial blood samples were drawn only at every second dose rate. For the 24-h infusion, the arterial catheter was, because of safety concerns, removed approximately 30 min after completion of the dose escalation. A new arterial catheter was inserted approximately 30 min before the end of the 24-h infusion, from which arterial blood samples were collected until 60 min after cessation of the infusion. The venous blood samples were drawn from the arm contralateral to the arm in which the infusion was given, and the arterial samples were collected from the infusion arm.

One milliliter of blood was immediately transferred to preweighed test tubes containing 1 ml 10% sodium dodecyl sulfate solution, which on mixing immediately stopped further hydrolysis of the ester group.¹² The samples were weighed, frozen, and stored at -70°C until analysis. The blood was mixed with the sodium dodecyl sulfate-containing test tubes within 15 s after start of withdrawal of blood, and because of the relatively slow *in vitro* hydrolysis rate of clevidipine in blood from man,⁶ approximately 5 min, the blood sampling time was not corrected in the actual sampling time.

The clevidipine concentrations were determined by a method based on gas chromatography and mass spectrometry.¹³ The intraday coefficients of variation of blood standards were 1–4% at 2.5 nM and 4–9% at 0.1 nM. The limit of quantification was set at 0.1 nM.

Pharmacokinetic Analysis

The dose linearity was evaluated by linear regression analysis of the pooled mean arterial concentrations at steady state in association with the different dose rates.

Bi- and triexponential disposition models were fitted to each individual's arterial blood concentration *versus* time data. The actual sampling times were used in the analyses. Weighted least-squares nonlinear regression analysis was used to fit the model to the data. The computer program WinNonlin (version 1.1; Scientific Consulting, Apex, NC) was used, and the data were weighted as $1/C_{\text{pred}}^2$, in which C_{pred} is the model-predicted blood concentration at the actual sampling times. The goodness of fit was evaluated by the Akaike information criterion¹⁴ residual plots, and visual inspection. The following pharmacokinetic parameters of clevidipine,

based on arterial blood concentrations, were calculated for each subject: blood clearance, initial volume of distribution and volume of distribution at steady state, half-lives, the fractional zero time intercepts (C_i) transforming data to a unit bolus dose, the fractional area (AUC_{λ_z}) associated with the terminal phase after a unit bolus dose and the contribution of this phase to the postinfusion area after attainment of steady state.¹⁵ The AUC_{λ_z} was calculated as

$$(C_z/\lambda_z)/\sum_{i=1}^{i=n} C_i/\lambda_i$$

where C_i and λ_i represent the fractional zero time intercept and the rate constant of the different phases, respectively, and the postinfusion area under the curve was calculated as

$$(C_z/\lambda_z^2)/\sum_{i=1}^{i=n} C_i/\lambda_i^2$$

Simulation of Decrement Times

The pharmacokinetic parameters determined after clevidipine infusion for 24 h at a final dose rate of $7 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ were used to simulate the decrement times for 50 and 90% decrease in the concentrations of clevidipine after different infusion times.^{16,17}

Statistical Analysis

Summary statistics are listed as the mean and SD for each pharmacokinetic parameter.

Results

Of the 15 randomized healthy volunteers, 12 completed the treatment and were evaluated regarding the pharmacokinetics and pharmacodynamics of clevidipine.

Pharmacokinetics of Clevidipine

There was a linear relation between the dose rate and the arterial blood concentrations of clevidipine at steady state, as shown in figure 2.

A triexponential disposition model gave the best fit to the individual arterial blood concentration *versus* time data according to the Akaike information criterion, residual plots, and visual inspection. The mean arterial and venous blood concentrations of clevidipine after intravenous infusion at a rate of $7 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$

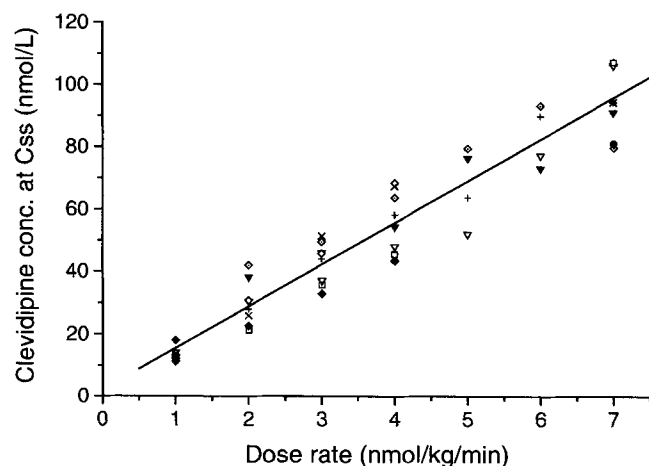


Fig. 2. Linear regression analysis of arterial concentrations of clevidipine at steady state (C_{ss}) versus dose rate, each symbol representing one subject. $C_{ss} = 2.13 + 13.38x$, $R^2 = 0.960$

over a 20-min period and the fit of the triexponential disposition model to the arterial blood concentration versus time data for a representative subject are shown in figure 3. The mean arterial and venous blood concentrations of clevidipine during dose titration to a final dose rate of $7 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and for a total infusion time of 24 h are shown in figure 4. The mean pharmacokinetic parameters of clevidipine are presented in table 1. The duration of the infusion had a negligible effect on the pharmacokinetics. The arterial mean blood clearance ranged between 0.066 and $0.075 \text{ l} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and the volume of distribution at steady state was between 0.14 and 0.22 l/kg . The high clearance and the

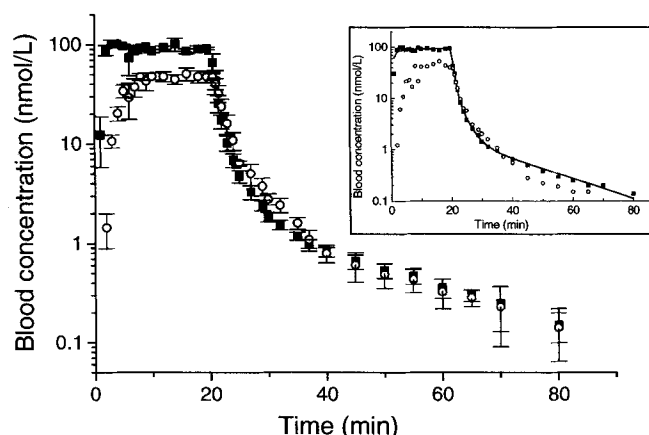


Fig. 3. Mean \pm SE arterial (squares) and venous (circles) blood concentrations of clevidipine after intravenous infusion at a rate of $7 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ over a 20-min period ($n = 4$). (Inset) Clevidipine concentrations in a representative subject. Solid lines show the fit of the three-compartment model to the arterial blood concentrations.

small volume of distribution resulted in extremely short half-lives. The half-lives of the two initial rapid phases, accounting for approximately 95% of the area under the curve after a unit intravenous bolus, ranged between 0.6 and 0.8 min and 2.2 and 2.3 min, respectively. The area under the terminal phase (half-life = 16–22 min) corresponded to 3.3 and 5.7% of the total area under the curve after an intravenous bolus. The corresponding contribution of this area to the mean postinfusion area after attainment of steady state was between 39 and 54%.

Decrement Times

The times to reach 50 and 90% postinfusion decreases in concentrations of clevidipine are shown in figure 5. The time to reach a 50% decrease in clevidipine concentrations was less than 1 min, regardless of the duration of the infusion, and the time to reach a 90% decrease in clevidipine concentration was approximately 5 min.

Effect on Mean Arterial Pressure and Heart Rate

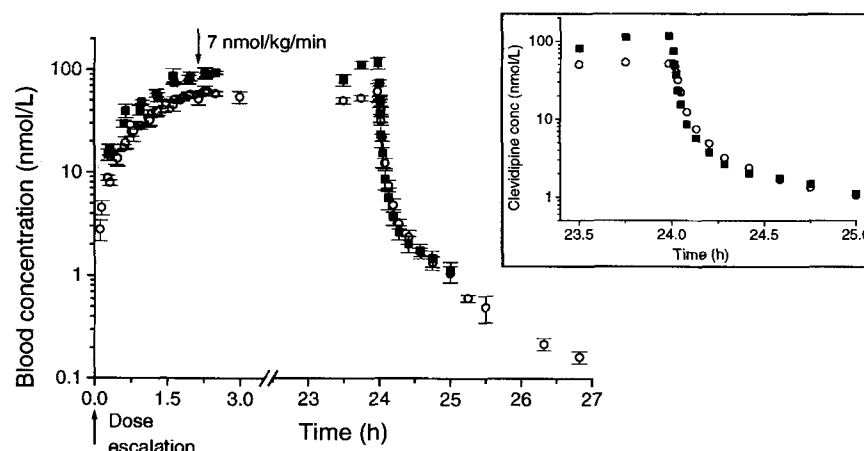
The mean arterial pressure (MAP) and heart rate, measured by Finapres cuff or sphygmomanometer, before, during, and after the short and 24-h infusions are shown in figure 6. The MAP and heart rate values obtained at the first measurement with the sphygmomanometer after cessation of the 24-h infusion, that is, 75 min after the end of the infusion, did not differ from those obtained at baseline, before start of infusion.

After the 20-min infusion and Finapres recordings, clevidipine reduced MAP from approximately 90 to 75 mmHg, and increased heart rate from approximately 53 to 75 beats/min, at steady-state conditions. After cessation of the infusion, MAP and heart rate returned to predose measurements within 10 min for all subjects. After approximately 1–2 h of continuous recording with the Finapres cuff, some subjects experienced pain and felt uncomfortable, and the cuff was loosened from the finger for various periods of times. Therefore, the effect recordings with the Finapres cuff during the long infusions are not reported.

Pharmacokinetic and Pharmacodynamic Relation

The pharmacodynamic responses expressed as percentage change from baseline values and the observed arterial and venous blood concentrations of clevidipine during and after a 20-min infusion of clevidipine in a representative subject are shown in figure 7. The figure shows that the time course of the arterial blood concentration is in good agreement with the rapid onset of the hemodynamic effects, with a very short time delay be-

Fig. 4. Mean \pm SE arterial (squares) and venous (circles) blood concentrations of clevidipine *versus* protocol sampling times after clevidipine administration for 24 h at a final rate of $7 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. (Inset) First hour after cessation of the infusion. $n = 4$.



tween the maximal arterial blood concentrations and the maximal effects. After cessation of the clevidipine infusion, the arterial and venous blood concentrations decreased rapidly. Initially, there was a more rapid decrease in the arterial concentrations; within 1 min the difference between the arterial and venous concentrations was negligible. The rapid recovery from drug action on MAP and heart rate lagged shortly behind the clevidipine concentrations.

Plotting the reduction in MAP or heart rate *versus* venous and arterial blood concentrations in time order resulted in clockwise and counterclockwise hysteresis loops, as shown in figure 8.

Discussion

The primary objectives of this study were to investigate the pharmacokinetics of clevidipine after a short- and a long-term infusion in healthy volunteers and to determine the relation between the arterial and venous blood concentrations, respectively, and the effects on MAP and heart rate. The dose rates of clevidipine used in

this study are equivalent to those used for perioperative reduction and control of blood pressure.^{11,18}

A nonenantioselective analytic method was used to determine the blood concentrations of clevidipine in the current study. However, the pharmacokinetic parameters of the separate enantiomers are essentially identical, suggesting that analyses of clevidipine, instead of the separate enantiomers, will result in similar pharmacokinetic parameters.¹⁹

In all three dose groups, a triexponential disposition model provided the best fit to the time course of the arterial blood concentrations of clevidipine. The duration of the intravenous infusion and the dose had negligible effects on the estimated pharmacokinetic parameters.

The initial half-life of clevidipine, determined from the arterial blood samples, was less than 1 min, and the arterial blood levels reached virtual steady state within 2 min. For the venous blood concentrations, steady state was achieved in approximately 10 min. However, after attainment of steady state in the arterial and venous blood, the arterial clevidipine concentrations were twice as high as the venous concentrations during ongoing

Table 1. Summary Pharmacokinetic Parameters for Clevidipine

Dose Rate and Duration	C ₁	C ₂	C ₃	CL (l · min ⁻¹ · kg ⁻¹)	V ₁ (l/kg)	V _{SS} (l/kg)	t _{1/2λ1} (min)	t _{1/2λ2} (min)	t _{1/2λ3} (min)	AUC _{λ2} (%)	AUC _{SSλ3} (%)
2 nmol · min ⁻¹ · kg ⁻¹ 24 h	0.867 (0.163)	0.130 (0.164)	0.003 (0.001)	0.072 (0.006)	0.10 (0.02)	0.20 (0.03)	0.7 (0.1)	2.2 (0.2)	18 (3)	5.4 (1.2)	50 (9)
7 nmol · min ⁻¹ · kg ⁻¹ 24 h	0.893 (0.072)	0.104 (0.071)	0.002 (0.001)	0.066 (0.005)	0.08 (0.02)	0.22 (0.08)	0.8 (0.3)	2.3 (0.1)	22 (2)	5.7 (2.4)	54 (11)
7 nmol · min ⁻¹ · kg ⁻¹ 20 min	0.942 (0.034)	0.056 (0.033)	0.002 (0.001)	0.070 (0.006)	0.07 (0.01)	0.14 (0.02)	0.6 (0.1)	2.3 (1.0)	16 (3)	3.3 (1.2)	39 (8)

Data are arithmetic mean (SD); $n = 4$.

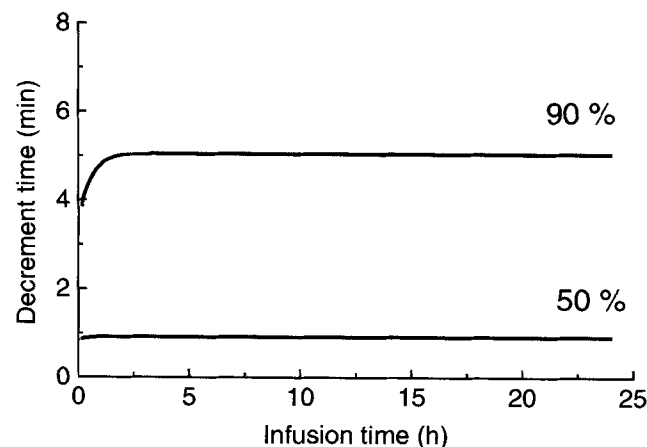


Fig. 5. The decrement times for 50 and 90% drops in clevidipine concentrations after increasing infusion times.

infusion for 24 h. This concentration difference reflects an irreversible loss of clevidipine as it passes through the microcirculation of the forearm. Furthermore, after cessation of the clevidipine infusion, the arterial concentrations decreased almost immediately to the same level as, and for a short period of time even below, the venous concentrations. Later on, the arterial blood concentrations became almost equal to the venous concentrations (figs. 3 and 4). These results indicate that clevidipine, in addition to being metabolized, also accumulates in some tissues during the transport across the arterial and venous capillary beds during ongoing infusion and then redistributes from these tissues into the blood upon cessation of the infusion. Thus, the venous postinfusion concentrations of clevidipine are the net results of metabolism and redistribution. In a previous study in which venous samples were obtained, clearance was half that in the current study.⁷ In that venous concentrations in the current study were approximately half of the arterial

concentrations, we expect estimates of clearance to differ twofold based on arterial *versus* venous sampling. Thus, the results of the previous study are consistent with those of the current study and demonstrate the importance of the sampling site for pharmacokinetic evaluation of drugs rapidly eliminated in peripheral tissues. Elimination of drug during the transfer of blood from the arterial to the venous site has also been described for other short-acting drugs such as esmolol, nitroglycerin, and sodium nitroprusside.^{8,20,21} For other drugs, this arteriovenous concentration difference has mainly been attributed to an initial tissue uptake.^{22,23}

The decrement times for 50 (context-sensitive half-time) and 90% postinfusion decreases in blood levels of clevidipine remain essentially constant for clevidipine at clinically relevant infusion times.^{16,17} The reason for this is that the initial rapid postinfusion decrease in clevidipine blood levels is primarily related to elimination,⁷ whereas the initial decrease in blood concentrations for most drugs after shorter infusions is caused by distribution to extravascular tissues.

The contribution of the terminal phase to the total area under the curve of clevidipine is approximately 5% after a unit intravenous bolus dose. The contribution of this phase to the postinfusion curve increased to approximately 50% after attainment of steady state. However, even if the terminal phase accounts for half of the area under the postinfusion curve and has a terminal half-life of approximately 20 min, the clevidipine concentration was less than 10% of the steady-state concentration within 5 min after cessation of the infusion because of the rapid elimination of clevidipine. These results confirm the minimal importance of terminal half-life in explaining the time course of drug effect.^{16,17,24}

A clockwise hysteresis loop was observed in plotting

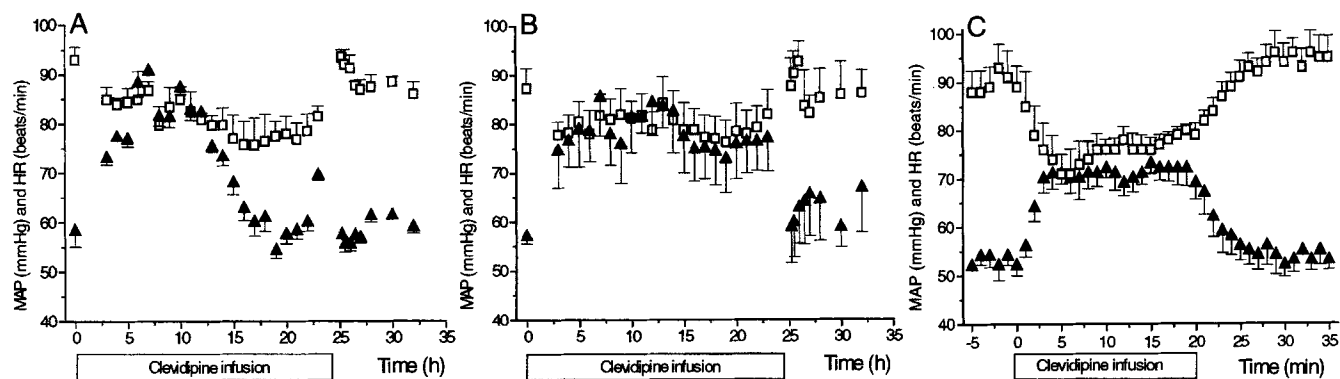


Fig. 6. Mean \pm SE arterial pressure (squares) and the heart rate (triangles) after clevidipine infusion for 24 h at a final infusion rate of $2 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (A), $7 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (B), or $7 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (C) for 20 min. $n = 4$.

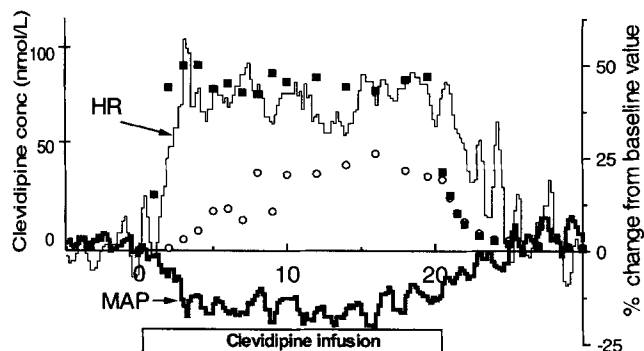


Fig. 7. The arterial (square) and venous (circle) blood concentrations of clevidipine left y-axis and the hemodynamic responses right y-axis in mean arterial pressure (thick line) and heart rate (thin line) before, during, and after cessation of a 20-min infusion of clevidipine at a rate of $7 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in a representative subject.

the effect *versus* venous concentration. One common explanation for this relation between the effect and venous concentration is development of acute tolerance. However, Gourlay and Benowitz²⁵ showed that acute tolerance to the chronotropic effects of nicotine was not apparent if arterial nicotine levels were measured instead of venous concentrations, and for drugs in which equilibrium between arterial concentrations and effect is faster than between arterial and venous concentrations, a clockwise hysteresis is expected.

Plotting the arterial concentrations *versus* the effect resulted in a counterclockwise hysteresis loop, which means that the arterial blood concentrations preceded the effect. The short delay between arterial blood con-

centration and effect may reflect distribution from the blood to the site of action, the calcium channels located in the vascular smooth muscle tissues.²⁶ However, the equilibrium time may also include a pharmacologic delay, that is, a hemodynamic equilibrium time as well as a distribution time.

The hemodynamic responses after long-term infusion with a blood pressure-reducing agent such as clevidipine are likely to be counter-regulated by several control mechanisms.²⁷ Furthermore, the rates of infusion of other calcium antagonists have been reported to affect the hemodynamic responses.^{28–30} To describe the effect of calcium antagonists, Francheteau *et al.*³⁰ proposed a physiologic model in which the essential features of the cardiovascular regulation were included in a closed-loop system. A control variable, primarily thought to reflect the role of the baroreceptor reflex, was included in the model. In addition, different pharmacokinetic and pharmacokinetic-pharmacodynamic models have also been proposed in the literature, in which an equilibrium delay described by a first-order rate constant has been included to account for the distribution process between the arterial and venous compartments, as well as between the arterial and effect compartments.^{31–34} The effect recording used in the current study and the size of the population studied did not allow for further evaluation of the concentration-effect relation after clevidipine infusion. However, the data presented in this study give a good estimate of how rapidly the effect of clevidipine can be titrated to a desired blood pressure level.

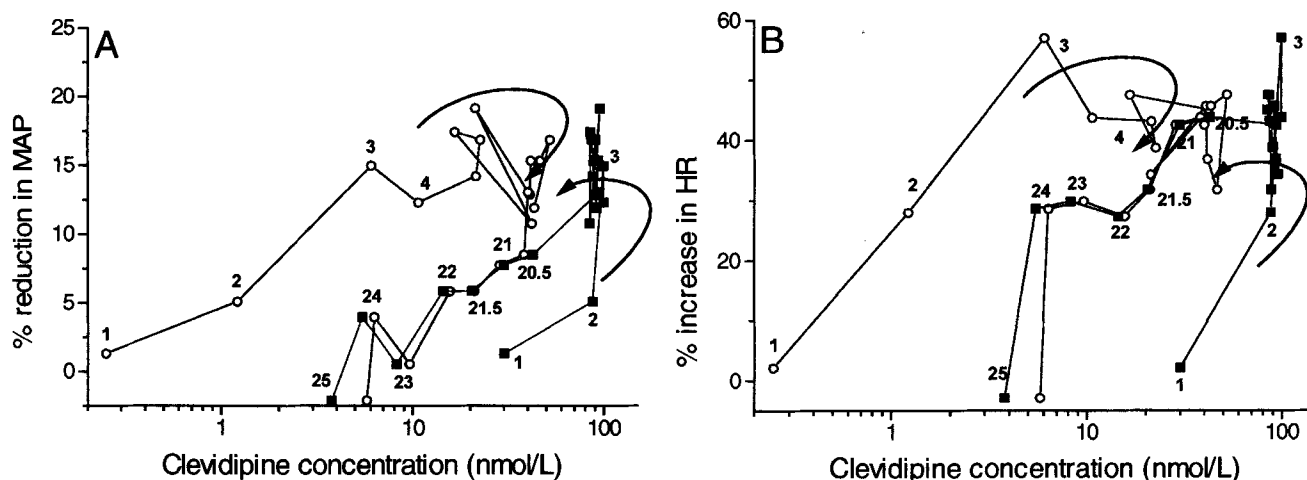


Fig. 8. The reduction in mean arterial pressure (A) and increase in heart rate (B) *versus* arterial (square) and venous (circle) blood concentrations of clevidipine after clevidipine infusion at a rate of $7 \text{ nmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ over a 20-min period to a representative subject. The data are plotted in time order and the numbers refer to the time (in min) after the start of the infusion; mean arterial pressure and heart rate are expressed as changes from baseline values.

In conclusion, clevidipine is a high-clearance drug with a small volume of distribution. The initial rapid increase in the arterial blood concentrations and the short equilibrium time between the blood and the bio-phase suggest that clevidipine can be rapidly titrated to the desired effect. During infusion for up to 24 h the arterial clevidipine concentration remains approximately twice as high as the venous level after attainment of steady-state concentrations in the two blood pools. The current study shows the importance of taking these arteriovenous differences into account in the pharmacokinetic and pharmacodynamic analysis.

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PHARMACOKINETICS OF CLEVIDIPINE

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