Pharmacokinetics and pulmonary extraction of clevidipine, a new vasodilating ultrashort-acting dihydropyridine, during cardiopulmonary bypass

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Clevidipine is a new vascular-selective, calcium channel antagonist of the dihydropyridine type with an ester side chain susceptible to esterase metabolism. In healthy volunteers, it has high clearance (0.069 litres min⁻¹ kg⁻¹) with a small volume of distribution at steady state (0.19 litres kg⁻¹). The half-lives of the two initial rapid phases, accounting for approximately 95% of the area under the curve after an i.v. bolus, are 0.7 and 2.3 min, respectively. The aims of this study were to determine the pharmacokinetics and the pulmonary extraction ratio of clevidipine in patients undergoing cardiac surgery. Seventeen patients received clevidipine as an i.v. infusion before cardiopulmonary bypass (CPB), and eight of these patients were also given clevidipine during hypothermic CPB. Mixed venous and arterial blood samples were taken for pharmacokinetic analysis and calculation of pulmonary extraction ratio. A two-compartment pharmacokinetic model with zero-order input was used to describe the pharmacokinetics of clevidipine before and during CPB. Virtually identical concentrations in mixed venous and arterial blood suggest negligible pulmonary metabolism of clevidipine. The total blood clearance of clevidipine is extremely high (0.055 litres min⁻¹ kg⁻¹). During CPB, clearance of clevidipine was significantly reduced, to 0.03 litres min⁻¹ kg⁻¹ (P<0.005), probably as a consequence of reduced body temperature.

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An important aspect of cardiac anaesthesia is to maintain haemodynamic stability while patients are subjected to stimuli of various intensities. However, the anaesthetic regimen may not predictably attenuate the haemodynamic response to various stimuli in patients undergoing coronary revascularization, whether they are based on high doses of opioids or balanced techniques. Moreover, postoperative hypertension is a common event after coronary artery bypass grafting (CABG) surgery and is associated with subendocardial ischaemia, bleeding and cerebrovascular haemorrhage.

Of the drugs available to control and reduce arterial pressure during cardiac surgery, calcium antagonists, such as nicardipine, may be beneficial because of their favourable haemodynamic profile. However, the pharmacokinetic properties of these agents render their clinical use more difficult than that of other drugs, such as glyceryl trinitrate and sodium nitroprusside, whose effects can be easily controlled because of their very short half-lives and the predicted post-infusion decline in plasma concentration after various lengths of infusion.

Clevidipine is a new vascular-selective calcium channel antagonist of the dihydropyridine type. It is structurally related to another calcium antagonist, felodipine, but, because it contains an ester linkage, is rapidly metabolized by esterases in blood and extravascular tissues to its inactive carboxylic acid metabolite. Clevidipine is cleared quickly with a relatively small volume of distribution resulting in an extremely short half-life in healthy volunteers, essential hypertensive and postcardiac surgical patients. In vitro studies have shown that the elimination of clevidipine is reduced at lower blood

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temperatures.14 This suggests that elimination of clevidipine might be reduced during hypothermia in vivo, as are other ester-containing molecules, such as remifentanil and esmolol, which both have decreased clearance during hypothermic cardiopulmonary bypass (CPB).19,20

Although clevidipine has previously been shown to reduce and control arterial pressure effectively in essential hypertensive and anaesthetized patients after cardiac surgery,17,18 this was the first study in which clevidipine was administered to patients during cardiac surgery. The aims of this study were to determine the pharmacokinetics of clevidipine before and during hypothermic CPB and to determine the pulmonary extraction of clevidipine in patients undergoing CABG surgery.

Patients and methods
Following approval by the Local Research Ethics Committee, 20 patients were enrolled after giving written informed consent. All patients were scheduled for elective CABG surgery. The main exclusion criteria for taking part in the study were acute myocardial infarction within 30 days before the study, an ejection fraction of ≤0.35, heart rate ≥120 beats min⁻¹ and clinically significant hepatic or renal disease.

Antihypertensive treatment, except for beta-blockers, was stopped the night before surgery. All patients received a standardized anaesthetic regimen consisting of morphine 10–15 mg i.m. and scopolamine 0.2–0.4 mg i.m. as premedication, followed by midazolam 0.1 mg kg⁻¹, fentanyl 15 µg kg⁻¹ and pancuronium 0.15 mg kg⁻¹ i.v. for induction of anaesthesia, and isoflurane at a minimum of 1% end-tidal concentration for maintenance of anaesthesia. Isoflurane was administered in 60% oxygen and 40% air when off CPB and the oxygen/air ratio was adjusted to the best blood gases during CPB (α-stat management of pH).

All patients underwent mild hypothermic CPB (30°C) with standardized equipment, and diastolic cardiac arrest was induced with cold crystalloid cardioplegia. The CPB circuit was primed with 1.5 litres of crystalloid solution. A roller pump (Cobe Laboratories, Denver, CO, USA) generated non-pulsatile flow, and the flow rate during the hypothermic phase of CPB was 1.8 litres min⁻¹ m⁻². Blood was circulated through a hollow fibre membrane oxygenator (Maxima™; T; Medtronic, Anaheim, CA, USA) and gas flow was adjusted in order to maintain arterial blood at pH 7.4 (α-stat measurement). Catheters were inserted into the left radial artery (Inyte® Vialon® Becton Dickinson, Franklin Lakes, NJ, USA) and pulmonary artery (Swan-Ganz 7F; Baxter Healthcare Corporation, Irvine, CA, USA) via the right subclavian vein. Heart rate and arterial pressure were monitored for ≤15 h from the start of anaesthesia. Nasopharyngeal temperature and haematocrit were also recorded throughout surgery.

Clevidipine is a 20% lipid emulsion containing clevidipine 0.5 mg ml⁻¹. Syringes containing clevidipine were connected to a filter (Sterifix 5 µm; Braun, Melsungen, Germany) and a 15 cm extension line (polyethylene extension tube 15 cm; Vygon, Ecouen, France). The drug was infused into the right jugular vein by means of a calibrated syringe driver (P1000 syringe pump, Welmed; Braun Melsungen). An infusion of clevidipine was started if the mean arterial pressure (MAP) exceeded 90 mm Hg before CPB or 75 mm Hg during CPB. The starting rate was 0.7 µg kg⁻¹ min⁻¹ and the maximum rate allowed was 22 µg kg⁻¹ min⁻¹. The infusion rates were adjusted every 2 min in steps according to the judgement of the investigator in order to reduce arterial pressure to the target MAP (i.e. 70–75 mm Hg before CPB and 55–60 mm Hg during CPB). When the desired MAP was reached, the clevidipine infusion was kept constant for ≥10 min and then stopped. Sodium nitroprusside was used to control arterial pressure after cessation of the clevidipine infusion. If clevidipine was infused before CPB, the clevidipine infusion was interrupted for ≥20 min before starting CPB in order to allow a washout period of clevidipine.

Blood sampling and bioanalysis
Blood samples (2 ml) for clevidipine analysis were drawn from the left radial artery before infusion, at 8, 9 and 10 min of constant rate infusion and 0.5, 0.75, 1, 2, 3, 4, 6, 8 and 10 min after termination of the infusion. Arterial pulmonary blood samples were taken at 8, 9 and 10 min of constant rate infusion. In addition, blood samples were taken at 5 and 9 min of constant rate infusion from the in-flow (venous side) and out-flow (arterial side) of the CPB circuit.

The collected blood was rapidly transferred to pre-weighed test tubes containing 2 ml of 10% sodium dodecyl sulphate (SDS) which, on mixing, immediately stops hydrolysis of clevidipine.21 The samples were weighed and frozen within 1 h and stored at −70°C until analysis. The clevidipine concentrations were determined by a method based on gas chromatography/mass spectrometry.22 The linearity of the method during the assay period was estimated from five standard curves. The standard curves were linear within the concentration range 0.26–166 µg litre⁻¹. The mean intra-day coefficients of variation (CVs) of blood standards of clevidipine were 2.2–14.6% at 0.25 µg litre⁻¹ and 1.1–2.9% at 16.5 µg litre⁻¹. The lower limit of quantitation was set at 0.23 µg litre⁻¹.

Pharmacokinetic analysis
The population mean pharmacokinetic parameters of clevidipine were determined by non-linear mixed effect modelling using the software program P-PHARM (version 1.5; SIMED, Creteil, France).23 The time course of the clevidipine concentrations in the arterial blood was fitted to mono-, bi-, or tri-exponential disposition functions.

Initial analyses of the distribution of the residuals showed that the error variance was best described by a hetereo-
scedastic model ($1/C_{\text{pred}}^2$ where $C_{\text{pred}}$ is the predicted concentration) and this error model was used in all analyses. The goodness of fit was evaluated by the Akaike information criterion, log-likelihood values and visual inspection of residual plots. The blood clearance ($Cl_b^0$), initial volume of distribution ($V_1$) and the rate constants for drug transfer between the central and the peripheral compartment(s), $k_{12}$ and $k_{21}$, were considered as primary parameters with normal distribution. Thus, the population mean and an estimate of its variability were obtained for each of these parameters. Other reported pharmacokinetic parameters were calculated from the individual (Bayesian) parameter estimates using standard pharmacokinetic equations. In addition, steady-state blood clearance ($Cl_{b,ss}$) was calculated as $R_d/C_{ss}$, where $R_d$ was the infusion rate and $C_{ss}$ the steady-state concentrations calculated as the mean of the clevidipine concentrations during the infusion.

Pulmonary extraction was calculated by dividing the difference between mean pulmonary and mean radial artery clevidipine concentrations by the pulmonary artery concentrations and expressing the results as a percentage for each patient. The mean concentrations were calculated from all blood concentrations obtained during the clevidipine infusion.

Statistics

The population mean pharmacokinetic parameters were estimated for the patients treated before ($n=17$) and during CPB ($n=8$). In order to compare the individual pharmacokinetic parameters before and during CPB, the statistical analysis was restricted to the eight patients who received clevidipine both before and during CPB. The pharmacokinetic parameters were analysed by paired Student’s $t$-test; $P<0.05$ was considered significant. Results are expressed as mean (SD).

Results

Twenty patients undergoing CABG were enrolled in this study. In three patients, arterial pressure did not rise above the inclusion level; thus, 17 patients completed the treatment and were evaluated regarding the pharmacokinetics of clevidipine. Eight of these were also treated with clevidipine during CPB. The pulmonary extraction ratio was only determined in 16 patients since blood sampling was accidentally omitted in one patient. The minimum infusion time was 10 min and the actual infusion time was 10, 11 or 13 min. However, blood samples for clevidipine determination were always collected 10 min after infusion. The physical characteristics of the patients are shown in Table 1.

A bi-exponential disposition model was used to describe the pharmacokinetics of clevidipine before and during CPB. The mean population fit and the individual fit of this model to the data obtained from patients before CPB ($n=17$) are shown in Figure 1(A), where the data are normalized to a dose rate of 1.4 µg kg$^{-1}$ min$^{-1}$. The population-predicted versus observed clevidipine concentrations are shown in Figure 1(B). The corresponding plots for the eight patients treated with clevidipine during CPB are shown in Figure 1(C) and the goodness of fit in Figure 1(D). The individual fits, based on Bayesian parameter estimate, of a two-compartment model to the clevidipine concentration–time data in patients receiving clevidipine both before CPB and during hypothermic CPB ($n=8$) are given in Figure 2.

The mean pharmacokinetic parameters of clevidipine determined in all patients before CPB and in the patients receiving clevidipine both before and during hypothermic CPB are given in Table 2. Mean (SD) $Cl_b$ during CPB (0.03 (0.005) litres min$^{-1}$ kg$^{-1}$) was significantly lower than that before CPB (0.058 (0.014) litres min$^{-1}$ kg$^{-1}$), whereas mean (SD) $V_{ss}$ was similar under both conditions (0.11 (0.04) and 0.12 (0.03) litres kg$^{-1}$, respectively). As a consequence of the reduced clearance and the unchanged volume of distribution, the resulting half-lives were significantly longer during hypothermic CPB than during CPB. The $\alpha$ and $\beta$ half-lives of clevidipine were 0.6 (0.2) and 3.8 (0.2) min before CPB and 1.3 (0.5) and 7.5 (1.1) min during CPB, respectively.

The individual mean radial and pulmonary artery concentrations obtained during clevidipine infusion are shown in Figure 3. The pulmonary extraction ratio was 3.9 (8.3) %, suggesting negligible or no pulmonary metabolism of clevidipine. In addition, there was no extraction of clevidipine by the extracorporeal circuit, since the difference in clevidipine concentration between the aortic and venous cannulae of the CPB circuit was 1.5 (4.7) and -1.4 (3.9) µg litre$^{-1}$ at 5 and 9 min, respectively.

Before CPB, the MAP at the start of treatment was 97 (6) mm Hg, and during CPB, the mean (SD) MAP at the start of treatment was 73 (10) mm Hg. Treatment was started during CPB in one patient at 72 mm Hg as this was judged clinically appropriate.

The infusion rate required to control arterial pressure before CPB and during hypothermic CPB was 2.2 (0.9) and 1.3 (0.4) µg kg$^{-1}$ min$^{-1}$, respectively.

Before CPB, the heart rate was 72 (13) and 75 (17) bpm before and at the end of clevidipine infusion, respectively. There was no difference in heart rate response whether or not the patient was treated with a beta-blocker ($n=11$ and $n=6$, respectively).

| Table 1 Physical characteristics of the 17 patients studied; mean (SD) values are given for age, height, weight and body mass index (BMI) |
|----------------|----------------|
| Gender: males/females | All patients | During CPB |
| Age (years) | 62 (44–76) | 65 (44–76) |
| Height (cm) | 174 (6) | 173 (7) |
| Weight (kg) | 81 (14) | 75 (16) |
| BMI (kg m$^{-2}$) | 27 (4) | 25 (5) |
| Beta-blocker treatment | 11 | 6 |
Fig 1  The mean population fit (thick black line) and the individual fit (dashed lines) of a two-compartment model to the clevidipine concentration–time data (A) before CPB (n=17) and (C) during hypothermic CPB. The data are dose-normalized to a dosing rate of 1.4 µg kg⁻¹ min⁻¹ over a 10 min period. The goodness of fit is shown for data before CPB (B) and during CPB (D) and the solid line represents line of identity.

Fig 2 Observed blood concentration of clevidipine and the model-predicted concentrations, in eight patients receiving clevidipine before CPB (A) and during hypothermic CPB (B). Each symbol in both graphs represents the same patient and the solid lines show the fit, based on Bayesian parameter estimate, of the model to the data. In one patient (open triangle) in which infusion lasted for 13 min, more than the recommended number of blood samples were taken and all concentrations were included in the analysis.

During bypass, nasopharyngeal temperature decreased from 34.9 (0.5) °C to 30.8 (1.5) °C, and the haematocrit decreased from 34 (5) % to 28 (4) % because of haemodilution.
Table 2 The mean and SD pharmacokinetic parameters, calculated from Bayesian parameter estimates and steady-state concentrations, of clevidipine determined in all 17 patients before CPB (A) and in the eight patients receiving clevidipine both before (B) and during (C) hypothermic CPB; AUCA is the contribution of the initial AUC to the total area following a unit i.v. dose; ** significantly different from pre-CPB (*P<0.05, **P<0.005)

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Discussion

Haemodynamic variations are common during cardiac surgery, as surgical stimuli will vary dramatically throughout the operation. The use of short-acting drugs to control arterial pressure during cardiac surgery has practical advantages. It allows rapid titration to the desired effect, as the drug rapidly attains steady-state concentrations in the blood after initiation of an i.v. infusion. Furthermore, the effect on arterial pressure is negligible shortly after termination of the infusion, which may obviate the need for vasopressors to compensate for the remaining vasodilating effect.

All calcium antagonists currently used in perioperative care have been developed for oral use. As a class, the dihydropyridines exert reasonably homogeneous haemodynamic effects, which are of importance in the treatment of angina pectoris, hypertension and cardiac failure. However, attention has not been focused on the development of calcium antagonists with a pharmacokinetic profile suitable for controlling the rapid changes in arterial pressure that may occur during cardiac surgery.

Clevidipine is a new ultrashort-acting dihydropyridine calcium antagonist developed for controlling arterial pressure during cardiac surgery. It is metabolized by blood and tissue esterases and its short half-life has been confirmed in both in vitro studies and in humans.

The pharmacokinetics of clevidipine calculated from arterial blood concentrations before CPB in the present study were in agreement with the pharmacokinetic parameters reported for clevidipine in normothermic patients after CABG surgery and in healthy volunteers after arterial blood sampling. Blood clearances calculated from the steady-state concentrations of clevidipine and the model-dependent estimate were virtually identical before CPB, whereas the model-dependent estimated blood clearance was slightly lower than that determined from steady-state concentrations during CPB. Plausible explanations for the discrepancy in the clearance value during CPB may be the short sampling period or that steady state was not achieved, or both. The latter seems unlikely since the arterial blood concentrations of clevidipine are at steady state within 2 min of starting an infusion in healthy subjects. However, the reduction in blood clearance of clevidipine during hypothermic CPB is in agreement with in vitro studies in human blood, in which the in vitro half-life increased from approximately 6 min at 37°C to 11 min at 30.5°C. In the same study, diluting the blood with an equal amount of Ringer–glucose solution did not affect the in vitro half-life of clevidipine in human blood, suggesting that the reduced clearance during CPB is mainly a result of reduced temperature, and not of haemodilution during this procedure. However, factors such as the non-pulsatile flow generated by CPB equipment, reduced cardiac output and a corresponding change in perfusion may also contribute to the lower blood clearance of clevidipine during CPB.

Interestingly, the blood concentrations needed to control arterial pressure during the different phases of cardiac surgery were approximately the same, that is the lower dose rate needed during CPB was caused by the reduced clearance of clevidipine.

As clevidipine undergoes extensive extravascular metabolism, the use of a two-compartment model with elimination only from the central compartment might be schematically incorrect, and we cannot exclude the possibility of peripheral hydrolysis of clevidipine. A model allowing elimination from both the central and peripheral compartment would
probably predict a larger volume of distribution at steady state. However, without \textit{a priori} knowledge of the exit rate constants from such a model, it is not possible to estimate the volume of distribution at steady state, since such a model is mathematically indistinguishable from the classic two-compartment mammary model with elimination only from the central compartment. Irrespective of the model fitted to the blood concentration–time profiles of clevidipine, the estimate of blood clearance will not be affected.

The contribution of blood metabolism of clevidipine to the total elimination is <10%, indicating high esterase activity in extravascular tissues. The present study suggests that extraction in the lungs is negligible, thereby ruling out the lungs as a major organ of elimination of clevidipine. These results are also in agreement with the ultrashort-acting opioid remifentanil, which is not extracted by the pulmonary circulation. As the blood clearance is approximately three times the average liver blood flow and close to the cardiac output in healthy subjects, other tissues besides the liver are likely to contribute to the elimination of clevidipine. Results from studies with the ester-containing compounds remifentanil and cisatracurium have indicated that liver impairment does not affect the total elimination of these drugs.

In healthy volunteers, arterial pressure reduction caused by clevidipine is accompanied by an increase in heart rate but that was not reported in anaesthetized patients after cardiac surgery. In the present study, there was no increase in heart rate when arterial pressure was reduced by clevidipine. This was true even in patients who were not receiving beta-blocker pretreatment, in whom a baroreceptor reflex-mediated change in heart rate could have occurred. The lack of heart rate increase during arterial pressure reduction in anaesthetized cardiac surgery patients but not in conscious volunteers is likely to be a result of depressed baroreceptor reflex sensitivity during anaesthesia.

In conclusion, clevidipine has high clearance and effectively controls arterial pressure during CABG surgery both before and during hypothermic CPB. A higher dosing rate of clevidipine is required to control arterial pressure before CPB than during hypothermic CPB, probably as a consequence of reduced clearance of clevidipine during hypothermia.

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Conflict of interest

H. Ericsson, Å. Jolin-Mellgård and M. Nordlander are employees of AstraZeneca R&D Mölndal. This work was supported financially by AstraZeneca.

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