

# Clevidipine in Adult Cardiac Surgical Patients

## A Dose-finding Study

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**Background:** Treatment of elevated blood pressure is frequently necessary after cardiac surgery to minimize postoperative bleeding and to attenuate afterload changes associated with hypertension. The purpose of this study was to investigate the pharmacodynamics and pharmacokinetics of a short-acting calcium channel antagonist, clevidipine, in the treatment of hypertension in postoperative cardiac surgical patients.

**Methods:** Postoperative cardiac surgical patients were randomized to receive placebo or one of six doses of clevidipine. Hemodynamic parameters were recorded and blood samples were drawn for determination of clevidipine plasma concentrations during infusion and after discontinuation of clevidipine. The concentration-response relation was analyzed using logistic regression, and pharmacokinetic models were applied to the data using population analysis.

**Results:** There were significant decreases in mean arterial blood pressure and systemic vascular resistance at doses greater than or equal to  $1.37 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . There were no changes in heart rate, central venous pressure, pulmonary artery occlusion pressure, or cardiac index with increasing doses of clevidipine. The clevidipine  $C_{50}$  value for a 10% or greater decrease in mean arterial pressure was  $9.7 \mu\text{g/l}$  and for a 20% or greater decrease in mean arterial pressure was  $26.3 \mu\text{g/l}$ . The pharmacokinetics of clevidipine were best described with a three-compartment model with a volume of distribution of 32.4 l and clearance of 4.3 l/min. The early phase of drug disposition had a half-life of 0.6 min. The context-sensitive half-time is less than 2 min for up to 12 h of administration.

**Conclusion:** Clevidipine is a calcium channel antagonist with a very short duration of action that effectively decreases systemic vascular resistance and mean arterial pressure without changing heart rate, cardiac index, or cardiac filling pressures.

IN patients undergoing cardiac surgery, a sudden increase in systemic blood pressure in the postoperative period is viewed as a clinical problem that requires treatment. Blood pressure increases cause increases in myocardial work, which may be poorly tolerated by a

heart with systolic dysfunction. An acute increase in the afterload to the left ventricle may cause a reduction in the stroke volume, an elevation in the left ventricular filling pressure, and pulmonary congestion.<sup>1</sup> An elevation in ventricular filling pressure reduces the gradient for subendocardial myocardial perfusion and can provoke ischemia.<sup>2</sup> Bleeding from surgical sites will be increased in the presence of undesired blood pressure elevation, and severe hypertension may cause sutures to pull through diseased arterial tissue, resulting in catastrophic bleeding.<sup>3</sup>

For these reasons, blood pressure elevations after cardiac surgery that may not fit a clinical definition of "hypertension" are undesirable and potentially unsafe. In the present article, this unintended elevation in blood pressure is referred to as "hypertension." The treatment of hypertension can be accomplished with many different pharmacologic modalities, each of which has significant benefits and disadvantages. Additional anesthetic or sedative drugs are not an option if the patient is awake postoperatively.  $\beta$ -adrenergic-blocking drugs can depress cardiac function, and currently available  $\alpha_1$ -blocking and  $\alpha_2$ -agonist drugs are difficult to use and are unpredictable in the acute setting.

Although direct-acting vasodilators are usually chosen for the acute treatment of hypertension in patients with cardiac disease, no one drug is ideal. The nitroso-vasodilators (nitroglycerin, nitroprusside) dilate venous capacitance vessels and decrease preload.<sup>4</sup> Currently available calcium channel-blocking drugs and hydralazine are not readily reversible. The nitroso-vasodilators, hydralazine, and fenoldopam are all associated with reflex tachycardia.<sup>5,6</sup> The ideal agent would be an arterial-specific vasodilator that has a rapid onset and offset, a low incidence of toxicity, and does not cause reflex tachycardia.<sup>7</sup>

The investigational drug clevidipine is a new calcium antagonist of the dihydropyridine class and has been recommended for reduction of blood pressure in the perioperative setting. Like two other dihydropyridines, felodipine and isradipine, clevidipine shows the property of vascular selectivity, *i.e.*, dilation of arteriolar resistance rather than inhibition of myocardial contractility.<sup>6</sup> In addition, clevidipine, like most dihydropyridines, appears to have no effect on venous capacitance vessels.<sup>8</sup> Its rapid offset of effect can be attributed to an ester link in its structure that may be rapidly hydrolyzed by esterases in blood and extravascular tissues.<sup>9</sup> Clevidipine has been shown to have a high clearance and

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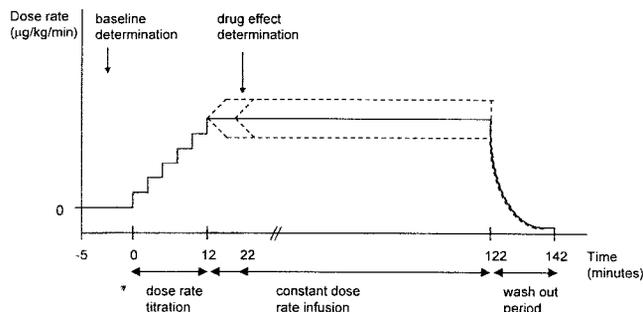
small volume of distribution, resulting in a half-life of 1–3 min in animal species, healthy volunteers, essential hypertensive patients, and surgical patients.<sup>10–11</sup> The purpose of this study was to investigate the pharmacodynamics and pharmacokinetics and to find the therapeutic dose interval of clevidipine in patients after cardiac surgery.

## Methods

After obtaining approval from the institutional review boards of Emory University School of Medicine (Atlanta, GA), Mount Sinai School of Medicine (New York, NY), Wake Forest University School of Medicine (Winston-Salem, NC), Temple University School of Medicine (Philadelphia, PA), and Kaiser-Permente Medical Center (San Francisco, CA), and written informed consent, patients scheduled for coronary artery bypass graft or valve replacement surgery were enrolled in the study. Entry criteria were age 18–80 yr, left ventricular ejection fraction greater than 30%, and planned use of a pulmonary catheter during and after surgery. Patients were ineligible for the study if they had suffered an acute myocardial infarction within 24 h before the start of the study, were women of childbearing potential, had histories of clinically significant hepatic or renal disease, had a ventricular pacemaker or a preexisting left bundle block, had a known intolerance to calcium channel blockers, or had allergies to soya bean or egg lecithin (components of the vehicle).

On admission to the intensive care unit postoperatively, consented patients were sedated with intravenous propofol at a dose determined at the discretion of the attending physician in the intensive care unit. However, the propofol dose was not varied during the period of clevidipine titration or the 10-min steady state infusion period around which hemodynamic variables used for analysis were recorded. Patients in the intensive care unit were eligible for randomization within the protocol if they had a mean arterial blood pressure (MAP) greater than 90 mmHg on two consecutive readings separated by 5 min. Randomization would not occur, and the patient would be excluded from study if she or he had a supine heart rate greater than or equal to 120 beats/min, had excessive mediastinal bleeding, an intraaortic balloon pump, or were receiving in excess of 4  $\mu\text{g}/\text{min}$  epinephrine, 5  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  dopamine or dobutamine, 50  $\mu\text{g}/\text{min}$  of nitroglycerine, any phosphodiesterase inhibitor, or other antihypertensive.

Patients were randomized to receive either placebo or one of four different doses of clevidipine (0.32, 1.37, 3.19, or 9.58  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). Because of a greater hemodynamic response than anticipated at these doses,



**Fig. 1.** An outline of the study design. Clevidipine was titrated to the randomized dose during the first 12 min of the study. The hemodynamic effects of this dose were observed for the next 10 min and the dose to the next highest or the next lowest if mean arterial pressure was greater than 105 mmHg or less than 65 mmHg, respectively, during the observation period.

the protocol was subsequently modified to also include randomization to doses of 0.05 and 0.18  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The protocol is shown in figure 1. Each study began with a 12-min titration phase, during which the investigator gradually increased the infusion rate to reach the randomized dose. The hemodynamic effects of this dose were observed from 12 to 22 min of infusion, during which the dose was increased (once) to the next highest dose if MAP was greater than 105 mmHg or decreased (once) to the next lowest dose if MAP was less than 65 mmHg. Patients who had a MAP greater than 105 mmHg or less than 65 mmHg after one change in infusion rate (or if they had MAP greater than 105 mmHg while receiving 9.58  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  or less than 65 mmHg with placebo) were removed from the study. After this 22-min dose-finding phase, the patients received the resultant dose at a fixed rate for the next 100 min, as long as MAP was between 75 and 95 mmHg (otherwise the patient was removed from the study). After 122 min (22 min for titration and 100 min of fixed-rate infusion), clevidipine was discontinued. Arterial blood samples (2 ml) were taken for analysis of clevidipine plasma concentrations 10, 18, 33, 48, 68, and 88 min after the start of the fixed-rate infusion and 0.5, 1, 1.5, 2, 3, 6, 12, 18, and 20 min after discontinuing clevidipine. After completion of this 20-min washout phase, patients requiring further antihypertensive therapy were given clevidipine at a dose that maintained MAP between 70 and 95 mmHg for up to 12 h. During this phase, blood samples were taken every 60 min.

Blood samples were quickly transferred to tubes containing sodium dodecyl sulfate and stored at  $-70^{\circ}\text{C}$ . Clevidipine concentrations were determined by gas chromatography—mass spectrometry. The lower detection limit of the assay was 0.2282  $\mu\text{g}/\text{l}$  with a relative SD of 2%.<sup>12</sup>

Hemodynamic data were analyzed by comparing the effect of dose on change (expressed as a percentage of baseline value) in heart rate, MAP, central venous pressure, pulmonary artery occlusion pressure, cardiac in-

dex, systemic vascular resistance (SVR), or pulmonary vascular resistance measured after 10 min of steady state infusion. Analysis was restricted to data from patients who did not require a change in dose during this 10-min interval. This interval was calculated to be sufficiently long to reach 90% of the steady state concentration based on previous pharmacokinetic studies of clevidipine.<sup>10</sup> Comparison was performed using the Kruskal-Wallis statistic with Dunn test for multiple comparisons. We also compared clinical responses at different doses using the chi-square statistic and an arbitrary definition of response as a 10% or greater change in MAP. We analyzed the relation between percentage change in MAP and plasma clevidipine concentration (measured after 10 min of steady state infusion) by determining whether patients had a 10% or greater decrease in MAP or a 20% or greater decrease in MAP at each measured concentration. This transforms the primary hemodynamic variable, change in MAP, to binary variables (> 10 or 20% reduction in MAP, yes or no). We then analyzed this transformed data by assuming that  $P_x$ , the probability of an x percentage or greater decrease in MAP, is given by the following equation:

$$P_x = C^{a(x)} / (C^{a(x)} + C_{50,x}^{a(x)}),$$

where C is the plasma concentration,  $C_{50,x}$  is the plasma concentration associated with a 50% probability of an x% or greater decrease in MAP, and  $a(x)$  is a parameter that determines the steepness of the concentration-effect relation and is a function of x. The pharmacodynamic parameters [ $C_{50,x}$  and  $a(x)$ ] were estimated with NONMEM, ignoring interpatient variability.<sup>13</sup>

Pharmacokinetic data were also analyzed with NONMEM, using both the first-order and conditional non-Laplacian (with centering) estimation techniques.<sup>13</sup> We assumed that each pharmacokinetic parameter had a log normal distribution. Expressed mathematically, we assumed that each parameter P for an individual patient was given by  $P = P_{TV} \exp(\eta)$ , where  $P_{TV}$  is the typical value of the parameter and  $\eta$  is a random variable with a normal distribution. Residual error (the difference between the predicted concentration [Cp] and the measured concentration [Cm]) was assumed to be either additive ( $C_m = C_p + \varepsilon$ ) or log normal [ $C_m = C_p \times \exp(\varepsilon)$ ], where  $\varepsilon$  is normally distributed.

We considered two- and three-compartment models, parameterized in terms of both compartment volumes and clearances (distribution and elimination). We compared a basic model (in which pharmacokinetic parameters were independent of weight) to a model in which the pharmacokinetic parameters were assumed to be proportional to weight. The optimal model was selected on the basis of the objective function ( $-2 \times$  logarithm of the likelihood of the results) using standard criteria.<sup>13</sup>

**Table 1. Demographics**

Age (yr)	63 (12)
Weight (kg)	81 (15)
Height (cm)	174 (9)
Sex	73 M/18 F

Data for age, weight, and height are presented as mean (SD).

## Results

Data were available for 85 of the 91 patients enrolled in the study. Six patients did not have hemodynamic data recorded because they required more than one dose change during the titration phase of the study. Each of these patients had been randomized to the highest dose ( $9.58 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) and required more than one dose change to achieve a MAP between 65 and 105 mmHg. Although each of these patients did achieve an acceptable MAP with further titration, the protocol stipulated *a priori* that these data would be excluded from the analysis. In addition, one patient randomized to the highest dose was mistakenly started at  $3.19 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and then the infusion was lowered to  $1.37 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  because of decreased MAP. Demographics are presented in table 1. The randomized doses and the actual doses used after titration of the study drug are shown in table 2. Plasma concentrations were available from 61 patients with a total of 577 samples.

Data for all hemodynamic parameters are shown in table 3. Figure 2 presents the individual values of MAP at baseline and after 10 min of infusion for each of the doses. Figure 3 presents comparable data for SVR. The changes in hemodynamic parameters with drug infusion were analyzed for significant differences among dose groups. Although 14 patients were randomized to receive  $9.58 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , only one patient actually received this dose, and this dose was removed from the analysis of variance. At the two higher doses of clevidipine, the reductions in MAP were significantly greater than those seen with the three lower doses and placebo, with the exception that the reduction in MAP with the  $1.37\text{-}\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  dose was not significantly differ-

**Table 2. Number of Patients by Randomized and Actual Dose Rates**

Randomized Dose ( $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	Actual Dose ( $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )							
	Placebo	0.05	0.18	0.32	1.37	3.19	9.58	NA
Placebo	2	—	—	9	—	—	—	—
0.05	—	6	5	—	—	—	—	—
0.18	—	—	11	2	—	—	—	—
0.32	1	—	—	6	3	—	—	—
1.37	—	—	—	4	7	1	—	—
3.19	—	—	—	—	12	6	—	2
9.58	—	—	—	—	1	8	1	4
Total	3	6	16	21	23	15	1	6

NA = study not completed; data not available.

**Table 3. Hemodynamic Parameters as a Function of Dose**

	Dose ( $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )					
	Placebo	0.05	0.18	0.32	1.37	3.19
HR						
Baseline	104 (12)	81 (5)	85 (10)	87 (12)	85 (9)	86 (12)
10'	104 (12)	82 (6)	86 (10)	88 (11)	85 (10)	86 (10)
MAP						
Baseline	93 (4)	94 (5)	101 (8)	101 (10)	100 (11)	103 (10)
10'	84 (18)	93 (6)	98 (4)	90 (19)	75 (18)	68 (15)
SVR						
Baseline	1,326 (202)	1,489 (202)	1,467 (322)	1,278 (383)	1,284 (386)	1,318 (332)
10'	1,108 (301)	1,403 (268)	1,354 (356)	935 (321)	810 (288)	864 (370)
PVR						
Baseline	78 (6)	188 (50)	144 (78)	161 (58)	125 (54)	136 (84)
10'	69 (97)	191 (64)	148 (74)	151 (61)	127 (50)	146 (58)
CVP						
Baseline	8 (2)	11 (4)	11 (4)	10 (3)	9 (3)	5 (2)
10'	8 (2)	12 (3)	10 (3)	10 (4)	10 (4)	8 (2)
PAOP						
Baseline	9 (3)	8 (3)	12 (4)	10 (4)	12 (3)	11 (3)
10'	9 (2)	11 (2)	12 (5)	10 (3)	11 (5)	12 (4)
CI						
Baseline	2.6 (0.4)	2.4 (0.3)	2.6 (0.5)	2.8 (0.5)	2.9 (0.6)	3.2 (0.9)
10'	2.7 (0.5)	2.5 (0.4)	2.6 (0.4)	3.2 (0.6)	3.3 (0.8)	3.1 (0.7)

The table presents mean hemodynamic parameters (SD) at baseline (for each dose group) and after a 10-min infusion at the indicated dose.

HR = heart rate (beats/min); MAP = mean arterial pressure (mmHg); SVR = systemic vascular resistance ( $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ ); PVR = pulmonary vascular resistance ( $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ ); CVP = central venous pressure (mmHg); PAOP = pulmonary artery occlusion pressure (mmHg); CI = cardiac index ( $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ).

ent that that with the  $0.05\text{-}\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  dose (table 4). At the two higher doses of clevidipine, the reductions in SVR were significantly greater than those seen with the two lower doses but were not significantly different than placebo (table 4). Heart rate, central venous pressure, pulmonary artery occlusion pressure, cardiac index, and pulmonary vascular resistance did not vary significantly with dose. Defining a clinical response as a decrease in MAP of 10% or more, we show the distribution of responders and nonresponders as a function of dose in table 5.

Figure 4 shows the relation between blood concentration of clevidipine and probability of a greater than x% (where x is 10 or 20) decrease in MAP, predicted by equation 1. Estimates of  $C_{50,x}$  and  $a(x)$  are given in table 6.

Pharmacokinetic data were described better by a three-compartment model with elimination from the central compartment than a comparable two-compartment model, with an improvement in the objective function of 188 units. The log-normal residual error model [ $C_m = C_p \times \exp(\varepsilon)$ ] was significantly better than the additive error model ( $C_m = C_p + \varepsilon$ ), with an improvement in the objective function of 44 units. Assuming that pharmacokinetic parameters were proportional to weight did not result in a statistically significant improvement in the fit.

The parameters of the optimal pharmacokinetic model are shown in table 6, along with the pharmacodynamic parameter estimates. (We present the pharmacokinetic parameter both as the weight-independent estimates of our optimal model and as values normalized to the mean

weight of patients in this study to facilitate comparison to other studies.) The normalized unit disposition function (the concentration after a unit bolus dose) for these pharmacokinetic parameters is:

$$C(t) = 0.947 \times \exp(-1.14 \times t) + 0.045 \times \exp(-0.133 \times t) + 0.008 \times \exp(-0.033 \times t),$$

where C is concentration and t is time in minutes. Figure 5 is a plot of  $C_m/C_p$  versus time for the optimal model. Prediction error ( $|(C_m - C_p)/C_p|$ ) was calculated for each data point, and median absolute prediction error for the entire data set was 0.313. We identified patients with the worst, median, and best individual median absolute prediction errors (0.712, 0.308, 0.101, respectively), and the relation between measured and predicted concentrations for these individuals is shown in figure 6.

## Discussion

The principal finding of the current study is that clevidipine is an effective agent to control elevated blood pressure after cardiac surgery. The mechanism of action appears to be predominantly a reduction in systemic vasculature with little or no effect on cardiac output. In this clinical setting, the drug is characterized by rapid kinetics and easy titratability, which may be attributed to rapid hydrolysis by plasma and tissue esterases.

Figure 2 suggests that an appropriate starting dose of clevidipine in this patient population would be between  $0.32$  and  $1.37 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Table 5 indicates that a

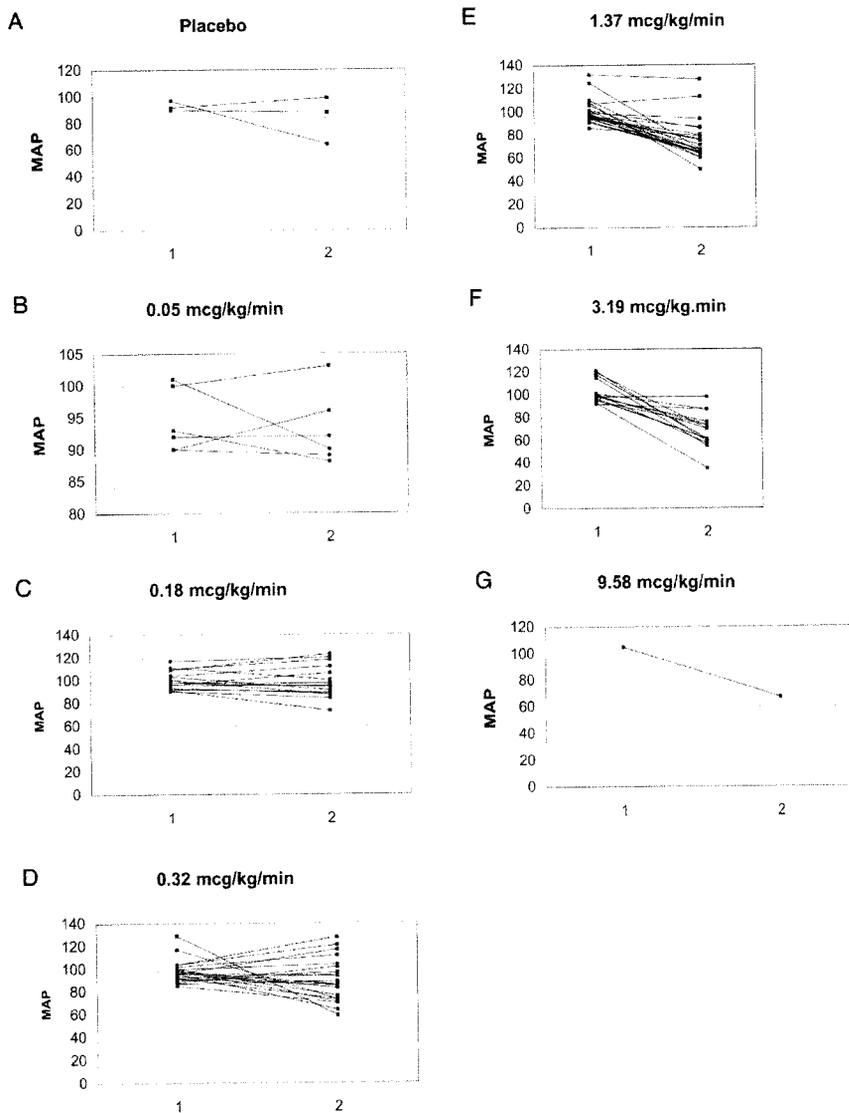


Fig. 2. (A–G) Values for baseline mean arterial pressure (MAP; denoted point 1) and MAP after 10 min of a constant-rate infusion (denoted point 2) for individual patients in each dose group.

significant rate of response occurs at a dose of  $0.32 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , when a positive response is conservatively defined as a decrease of MAP of 10% or more. We found that a clevidipine concentration of  $9.7 \mu\text{g}/\text{l}$  was associated with a 50% probability of a 10% or greater reduction in MAP. Using the elimination clearance estimate in table 6, this would be achieved at steady state by an infusion at  $41.7 \mu\text{g}/\text{min}$ , or approximately  $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for patients with the mean weight of those in this study. A clevidipine concentration of  $26.3 \mu\text{g}/\text{l}$  is associated with a 50% probability of a 20% or greater reduction in MAP, and this is more typical of the blood pressure reduction needed in cardiac surgical patients who have acute increases in blood pressure in the postoperative period. This concentration would be achieved at steady state by an infusion of  $114.09 \mu\text{g}/\text{min}$  or approximately  $1.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for patients with the mean weight of those in this study.

Previous studies of clevidipine have used both two- and three-compartment models.<sup>9–11</sup> The differences in

optimal models may be related to arterial *versus* venous sampling, as well as sampling schedules. We found that a three-compartment model was optimal, in agreement with the recent report by Ericsson *et al.*<sup>14</sup> using arterial sampling. Our estimate of central volume and elimination clearance is very similar to that reported by these investigators, although our estimate of volume of distribution at steady state is higher. Our results confirm that clevidipine is a high-clearance drug.<sup>9–11</sup> Although the terminal phase has a half-life of 21 min, the context-sensitive half-time is short ( $< 2$  min), as shown in figure 7. This figure also presents the time required for an 80% decrease in plasma concentration, which plateaus at approximately 10 min after 10 h of infusion. Figure 8 presents simulations of the concentrations that would result from infusions of  $0.5$  and  $1.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  using the pharmacokinetic parameters reported in table 5. The figure also indicates the concentrations associated with a 50% probability of achieving a minimum reduction in MAP of 10 or 20%. If the starting dose is

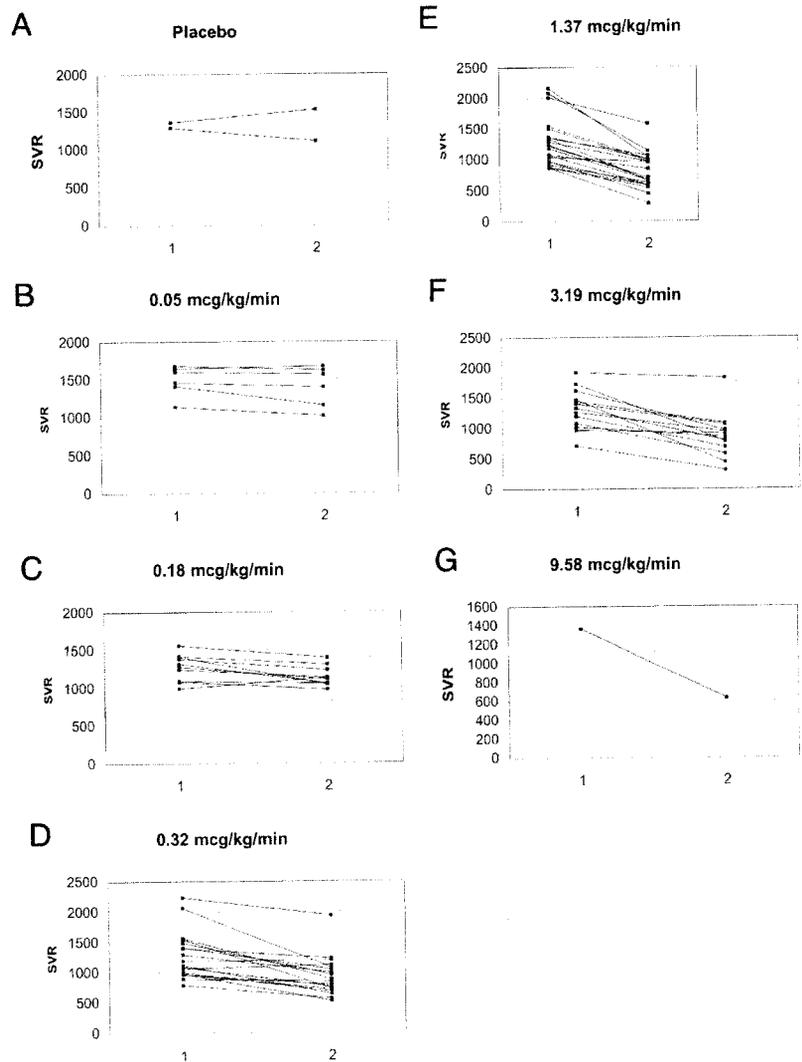


Fig. 3. Values for baseline systemic vascular resistance (SVR; denoted point 1) and SVR after 10 min of a constant-rate infusion (denoted point 2) for individual patients in each dose group.

1.4  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , the concentration associated with a 50% probability of a 10% or more decrease in MAP is very rapidly achieved, and the short context-sensitive half-time will facilitate subsequent titration to effect.

In contrast to previous studies, we did not find that adjusting for weight improved the quality of our phar-

macokinetic analysis. It is intuitive that larger individuals require a larger drug dose to achieve the same effect, and it is clear that body mass should be an important covariate in pharmacokinetic analysis. However, the range of weights in this study was relatively narrow, and this would make finding a statistically significant effect of

Table 4. Change in Hemodynamic Parameters as a Function of Dose

	Dose ( $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )					
	Placebo	0.05	0.18	0.32	1.37	3.19
$\Delta$ HR	0.7 (2.3)	0.4 (3.2)	-0.4 (2.4)	0.1 (7.8)	0 (8.2)	-2.8 (15.5)
$\Delta$ MAP	-3.0 (8.8)	1.2 (6.4)	3 (9.2)	7.5 (20.6)	25.5* (14.9)	32.7† (17.8)
$\Delta$ CI	3.6 (6.2)	4.4 (53.9)	1.1 (11.6)	16.8 (30.0)	11.1 (18.7)	0 (23.2)
$\Delta$ SVR	0.8 (22.9)	5.9 (9.8)	7.5 (12.0)	25.8 (17.4)	37.0‡ (13.9)	34.8‡ (21.3)
$\Delta$ PVR	7.4 (160.4)	-1.3 (61.2)	-14.5 (54.8)	1.4 (41.2)	-3.1 (54.2)	-15.9 (64.7)
$\Delta$ CVP	0.3 (0.2)	0.2 (0.2)	0.1 (0.8)	0.0 (0.9)	0.1 (0.5)	0.2 (0.8)
$\Delta$ PAOP	-0.2 (0.2)	0.6 (0.7)	0.2 (0.8)	0.0 (1.4)	0.1 (1.0)	0.1 (0.4)

HR = heart rate (beats/min); MAP = mean arterial pressure (mmHg); CI = cardiac index ( $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ); SVR = systemic vascular resistance ( $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ ); PVR = pulmonary vascular resistance ( $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ ); CVP = central venous pressure (mmHg); PAOP = pulmonary artery occlusion pressure (mmHg).

Data are presented as mean percentage decrease (MAP, SVR, PVR, CVP, PAOP) or increase (HR, CI) as a function of dose, with SD in parentheses.

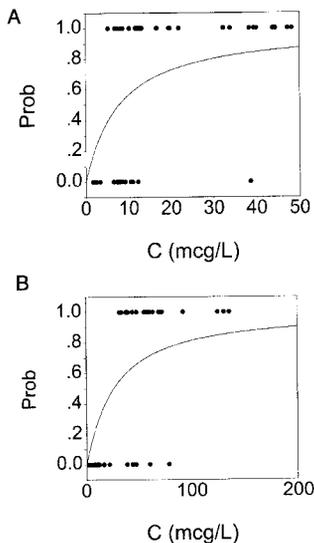
\* Changes in MAP significantly different from placebo, 0.18, and 0.32  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . † Changes in MAP significantly different from placebo, 0.05, 0.18, and 0.32  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . ‡ Changes in SVR significantly different from doses of 0.05 and 0.18  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ .

**Table 5. Response Rates as a Function of Dose**

Randomized Dose ( $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	Responders N (%)	Nonresponders N (%)	P Value (vs. Placebo)
Placebo	0 (0)	11 (100)	
0.05	1 (9)	10 (91)	0.500
0.18	4 (31)	9 (69)	0.067
0.32	6 (60)	4 (40)	0.004
1.37	9 (75)	3 (25)	< 0.001
3.19	19 (95)	1 (5)	< 0.001
9.58	14 (100)	0 (0)	< 0.001

weight on parameter estimates less likely. It would be prudent not to extrapolate our findings outside the weight range of our study population. We did not systematically investigate covariates other than weight as the original purpose of this study was dose-finding. Figure 5 demonstrates that the predictive error of the model increased during the washout phase. This could be a result of the influence of covariates not considered in our analysis, including a weight effect, that were only apparent during washout. It could also be a result of model misspecification, especially in the residual error model. However, multiple residual error models were considered during our analysis.

One striking differences between the hemodynamic results of this study and investigations in human volunteers and patients with essential hypertension is that we did not observe an increase in heart rate with the reduction in blood pressure. We did not control for intraoperative  $\beta$ -blocker administration, and 15 patients were



**Fig. 4.** The relation between clevidipine concentration (expressed as micrograms per liter) and the probability (Prob) of a 10% or greater (A) or 20% or greater (B) decrease in mean arterial pressure. The filled symbols at Prob = 1 or Prob = 0 indicate patients who did or did not fulfill these criteria at the indicated clevidipine concentration. The solid line is the probability predicted by the equation:

$$P_x = C^{a(x)} / (C^{a(x)} + C_{50,x}^{a(x)}),$$

using the pharmacodynamic parameters shown in table 6.

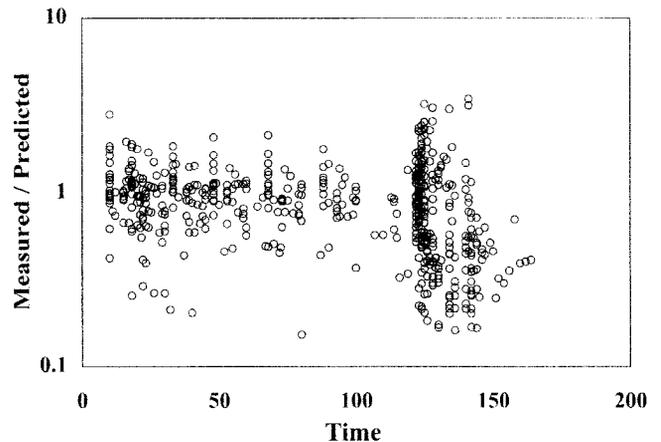
**Table 6. Pharmacokinetic and Pharmacodynamic Parameters**

Pharmacokinetic	
V1	6.08 (1.16) l or 0.075 l/kg
V2	8.91 (1.75) l or 0.11 l/kg
V3	17.4 (5.04) l or 0.21 l/kg
Cl1	4.3 (0.19) l/min or 0.053 l · kg <sup>-1</sup> · min <sup>-1</sup>
Cl2	1.62 (0.55) l/min or 0.02 l · kg <sup>-1</sup> · min <sup>-1</sup>
Cl3	0.678 (0.19) l/min or 0.008 l · kg <sup>-1</sup> · min <sup>-1</sup>
Pharmacodynamic	
C <sub>50,10</sub>	9.7 (0.32) $\mu\text{g/l}$
a(10)	1.00 (0.86)
C <sub>50,20</sub>	26.3 (7.26) $\mu\text{g/l}$
a(20)	1.09 (0.30)

V1, V2, and V3 are compartment volumes (V1 is the central compartment). Cl1 is elimination clearance, and Cl2 and Cl3 are distribution clearances from the central to the second and third compartments, respectively. Values in parentheses are standard errors. Pharmacokinetic parameters normalized to the mean weight of patients in this study are also shown.

being atrially paced; these factors may have contributed to the absence of reflex tachycardia. Another striking difference is that we saw a decrease in MAP at lower doses of clevidipine than in previous studies of healthy volunteers and essential hypertensive patients. In fact, the protocol was modified during the study to include the possibility of randomization to lower doses than originally planned. In addition, six patients randomized to the highest dose (9.58  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) required more than one dose change to achieve an acceptable MAP. These findings are consistent with the fact that cardiac surgical patients have altered physiology and are very sensitive to vasodilator drugs in the immediate postoperative period.

It is common for patients to require volume resuscitation in the first hours after cardiac surgery.<sup>15</sup> Ongoing blood loss and fluid redistribution caused by increased capillary permeability are partly responsible for this finding.<sup>16</sup> Hypertensive patients often mask hypovolemia with enhanced sympathetic tone, and these patients may respond dramatically to vasodilator administration.<sup>15</sup> The presence of sedative doses of propofol, a vasodila-



**Fig. 5.** The ratio of measured-to-predicted clevidipine concentration as a function of time. Concentrations were predicted with the pharmacokinetic parameters shown in table 6.

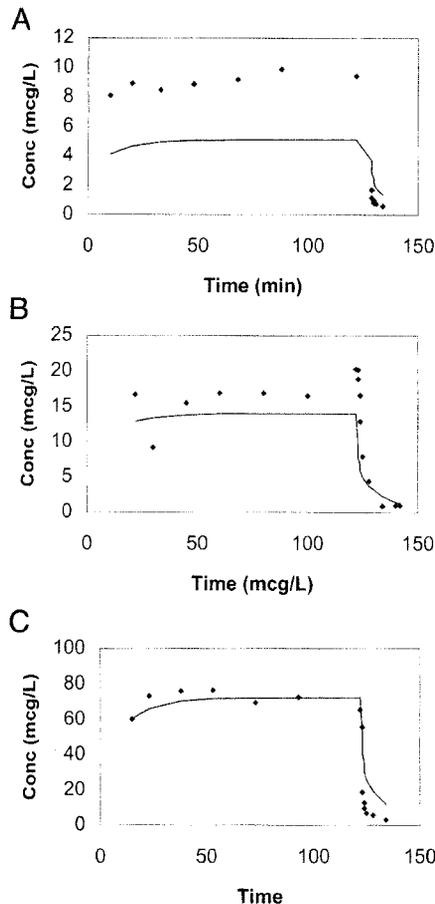


Fig. 6. The relation between measured (filled symbols) and predicted (solid lines) concentrations for the patients with the worst (A), median (B), and best (C) values of median absolute performance error.

tor,<sup>17</sup> may also have contributed to the sensitivity of these patients to clevidipine. The doses of propofol were determined by clinicians caring for the patients and were not controlled by the protocol, although propofol doses were not varied during the period of clevidipine titration and constant rate infusion bracketing the times of hemodynamic measurements. Propofol also blocks barorecep-

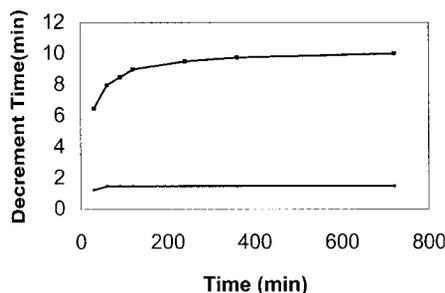


Fig. 7. Decrement times (time required for a given percentage decrease in blood concentration [Conc]) predicted for clevidipine using the pharmacokinetic parameters reported in table 6 as a function of time of infusion (to maintain constant blood concentrations during administration). The upper curve is the 80% decrement time, and the lower curve is the 50% decrement time, the context-sensitive half-time.

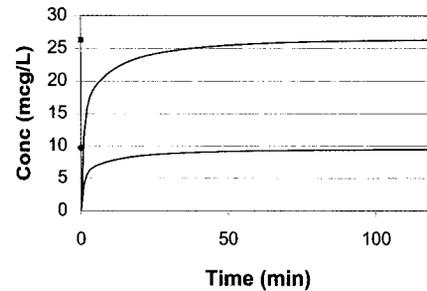


Fig. 8. Concentrations (Conc) of clevidipine predicted by the pharmacokinetic parameters reported in table 6 for infusions of 0.5 (lower curve) or 1.4 (upper curve)  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The symbols on the y-axis represent the concentrations associated with a 50% probability of a 10% or greater (filled triangle) or 20% or greater (filled square) decrease in mean arterial pressure.

tor responses,<sup>18</sup> which may explain the absence of a reflex tachycardia in our investigation and in previous investigations of clevidipine in patients undergoing coronary artery bypass graft.<sup>8</sup> Clevidipine has no significant direct effect on sinus node activity or atrioventricular nodal conduction.<sup>19</sup>

An expected result of decreased SVR is an increase in cardiac index, which was not observed in the current study. Absence of a reflex tachycardia may at least partly explain why there was no increase in cardiac index. Increases in cardiac index with other antihypertensive drugs in this setting have been associated with significant increases in heart rate.<sup>4,5</sup> Another explanation is that the current patient population with normal left ventricular function would not be expected to have afterload-dependent cardiac performance. However, in patients sedated with fentanyl after coronary artery bypass graft surgery, stroke volume did indeed increase when MAP was reduced with clevidipine. Furthermore, when MAP was reduced to an equal extent with either clevidipine or nitroprusside, stroke volume was higher with clevidipine than with nitroprusside.<sup>8</sup>

Although nitroprusside has been widely used for acute treatment of perioperative hypertension, its potent venodilating activity counteracts any potential increases in stroke volume caused by vasodilation and contributes to lability of blood pressure. Metabolism of the parent drug may cause cyanide toxicity. Intravenous nicardipine, another arterial-selective calcium-channel blocker, compares favorably to nitroprusside in terms of hemodynamic stability<sup>20</sup> and has a favorable therapeutic ratio, but has a duration of action of 10–20 min. Clevidipine appears to combine the beneficial hemodynamic effects and lack of toxicity associated with nicardipine, with the rapid onset and offset of nitroprusside. Fenoldopam, a dopamine-1 agonist, is an arterial dilator with a short duration of action, but reflex tachycardia is a prominent feature of this drug.<sup>21</sup> If further study of clevidipine confirms the absence of reflex tachycardia (*i.e.*, in the

absence of propofol), this drug may prove to be a more desirable agent for acute control of blood pressure.

In summary, in coronary artery bypass graft patients with hypertension after admission to the postoperative intensive care unit, clevidipine pharmacokinetics are similar to those measured in healthy volunteers. The drug shows rapid onset and offset of effect and has very rapid clearance. Pharmacodynamics include a dose-related and concentration-related decrease in blood pressure and SVR, with preservation of cardiac index and without reflex tachycardia. Clevidipine may be a useful drug in the treatment of acute postoperative hypertension.

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