Pharmacodynamic, Pharmacokinetic and Clinical Effects of Clevidipine, an Ultrashort-Acting Calcium Antagonist for Rapid Blood Pressure Control

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ABSTRACT

Clevidipine is an ultrashort-acting vasoselective calcium antagonist under development for short-term intravenous control of blood pressure. Studies in animals, healthy volunteers and patients have demonstrated the vascular selectivity and rapid onset and offset of antihypertensive action of clevidipine, a synthetic 1,4-dihydropyridine that inhibits L-type calcium channels. Clevidipine has a high clearance (0.05 L/min/kg) and is rapidly hydrolyzed to inactive metabolites by esterases in arterial blood. Its half-life in patients undergoing cardiac surgery is less than one min.

Unlike sodium nitroprusside, a drug commonly used for the short-term control of blood pressure, which dilates both arterioles and veins, clevidipine reduces blood pressure through a selective effect on arterioles. As documented in animals and in cardiac surgical patients, clevidipine reduces peripheral resistance without any undesirable effect on cardiac filling pressure. It increases stroke volume and cardiac output. In anesthetized patients undergoing cardiac surgery clevidipine, unlike sodium nitroprusside, does not increase heart rate.

In addition of having a favorable hemodynamic profile, suitable for rapid control of blood pressure, clevidipine protects against ischemia/reperfusion injuries, which are not uncommon during major surgery. In anesthetized pigs, clevidipine reduced infarct size after 45 min-long myocardial ischemia by 40%. In rats, renal function and splanchnic blood flow were better maintained when blood pressure was reduced with clevidipine than with sodium nitroprusside.
Clevidipine was well tolerated in Phases I and II of clinical trials that included more than 300 individuals/patients. Since there are no known compounds with similar pharmacodynamic and pharmacokinetic properties in clinical development, it is anticipated that clevidipine, a compound tailored to the needs of anesthesiologists, has the potential to become a drug of choice for controlling blood pressure during surgical procedures.

INTRODUCTION

Clevidipine is a vasoselective, short-acting dihydropyridine-type calcium antagonist. It is in development for the treatment of perioperative hypertension. Acute blood pressure elevation is frequently observed in the perioperative setting. Systemic hypertension after coronary artery bypass graft (CABG) surgery was first described by Estafanous et al. in 1973 as a sustained arterial pressure elevation (19). Perioperative hypertension generally results from activation of the sympathetic nervous system in combination with insufficient inhibition of nociceptive stimuli during anesthesia and surgery. This alteration in sympathetic nerve activity causes a peripheral vasoconstriction with an increase in systemic vascular resistance (SVR) while cardiac output (CO) decreases, increases or remains unchanged (24,51).

A prospective survey investigating therapeutic principles for the management of perioperative hypertension during cardiac surgery (52) indicated that more than 80% of patients required treatment to control blood pressure during surgery. Interestingly, the blood pressure level at which treatment was started ranged from 10 mm Hg above to 8 mm Hg below the preoperative blood pressure level, depending on the phase of the operation. In addition, blood pressure was maintained at levels that were 15–20% lower than the preoperative values. It was concluded that routine cardiothoracic anesthesia practice should be to reduce and maintain blood pressure at or below normal preoperative levels in order to prevent associated morbidities. The most commonly used drugs for controlling perioperative hypertension are nitroglycerin (GTN), sodium nitroprusside (SNP), β-adrenoceptor and calcium antagonists (51,52). Both GTN and SNP have a pharmacokinetic profile that allows rapid titration to the desired blood pressure level (40). However, these drugs are non-selective vasodilators, they dilate both arteriolar resistance as well as venous capacitance vessels (37,40). The latter effect may compromise venous return and thereby reduce cardiac output (CO) (24). In addition, SNP may induce side effects such as rebound hypertension at the cessation of infusion, coronary steal and potentially cyanide toxicity (24). Moreover, drug tolerance is a common concern with GTN or SNP (24,40).

The ultrashort acting β-adrenoceptor antagonist, esmolol, has commonly been used during perioperative hypertension in cardiac surgery (51). This drug has a high plasma clearance with a terminal half-life of approximately 10 min, allowing for titration to the desired level (35). However, β-adrenoceptor antagonists decrease blood pressure at least partly by reducing CO. They do not affect primarily increased SVR, the most common reason for elevated blood pressure during cardiac surgery (35,37,40). A potential drawback of reducing CO is impaired organ perfusion.

Dihydropyridine-type calcium antagonists, like nicardipine, isradipine and nifedipine, have been used successfully to control blood pressure during cardiac surgery (37). Among calcium antagonists, dihydropyridines are highly vasoselective; they dilate precapillary resistance vessels without depressing cardiac contractility (40,51). Calcium antagonists
Clevidipine appears to fulfill the criteria established on the basis of preclinical and clinical evidence discussed in this review. Further development of clevidipine is being currently conducted by The Medicines Company, Parsippany, New Jersey, USA.

CHEMISTRY AND FORMULATION

Clevidipine is a synthetic dihydropyridine selected for development on the basis of its vasoselective properties and short duration of action. It was selected after synthesis and screening of many dihydropyridines with easily hydrolyzable ester substituents. Clevidipine, butyroxyethyl methyl 4-(2',3'-dichlorophenyl)-1,4-dihydro-2,6-dimethyl, 3-5-pyridinedicarboxylate (Fig. 1), has a molecular weight of 456.3 g/mol. It is a racemic mixture, with a log $K_D$ estimated to be $\geq 5$. Both enantiomers have been synthesized and are equally potent with half-lives similar to that of clevidipine. Clevidipine is practically insoluble in water (0.1 mg/mL); therefore, a clevidipine emulsion in soybean oil was developed. The dosage form used in most clinical trials contains 0.5 mg clevidipine/mL.

PHARMACOLOGY

In Vitro Mechanism of Action Studies

Cellular action

Calcium antagonists exert their effects by inhibiting the transmembrane calcium influx through voltage-dependent L-type calcium channels. Dihydropyridines have a distinct binding site at the $\alpha_1$ subunit, which contains voltage-gated channel pore (55). Like other dihydropyridines, clevidipine decreases L-type calcium channel current in guinea pig myocytes (55). The magnitude of this inhibition is voltage-dependent. Clevidipine has
been shown to be three to six times more potent when the holding potential is raised to –40 from –80 mV. Because the resting potential of vascular smooth muscle cells is less negative than that of cardiac myocytes, this voltage dependence may in part explain why clevidipine selectively depresses contractility of vascular smooth muscle and thereby causes vasodilatation with a very limited impact on myocardial contractility (36).

**Vascular and cardiac effects**

The portal vein is a suitable *in vitro* model of the type of smooth muscle present in the arterial resistance vessels, since both exhibit spontaneous myogenic activity (38). Clevidipine is an equipotent inhibitor of spontaneous myogenic, neurogenic and agonist-induced contractions of the rat portal vein, suggesting a common inhibitory pathway (4). Clevidipine also causes dose-dependent relaxation of thromboxane A₂-induced contraction of arterial smooth muscle in *in vitro* preparations of intact and endothelial-denuded human internal mammary artery (28).

The inhibitory effects of clevidipine on myocardial contractility and on spontaneous heart rate were studied in isolated Langendorff-perfused rat hearts and compared to those of isradipine and nifedipine (47). In this setting nifedipine and isradipine, at high concentrations reduced heart rate and caused atioventricular block, while clevidipine was devoid of such effects at any concentration studied, although the maximal rate of pressure generation in the left ventricle \( \frac{dP}{dt_{\text{max}}} \) decreased at the highest concentration used. Thus, in contrast to nifedipine and isradipine, clevidipine did not interfere with spontaneous heart rate or AV conduction even at concentrations that reduced cardiac contractility by more than 50% (47).

In contrast to calcium antagonists of the phenylalkylamine (e.g., verapamil) and benzothiazepine (e.g., diltiazem) drug classes, dihydropyridines are more potent in relaxing vascular smooth muscle than in inhibiting myocardial contractility (38). The vascular versus myocardial selectivity of clevidipine was determined *in vitro* and compared to that of felodipine, a highly vasoselective antihypertensive dihydropyridine-type calcium antagonist (38). Selectivity was determined as the ratio between IC₅₀ for the contractility of a paced rat papillary muscle and for spontaneous activity of the portal vein mounted in the same organ bath. In accordance with previous reports (38), the vascular versus myocardial selectivity of clevidipine was 48 and that of felodipine was 126 (4). It was concluded that clevidipine is a highly vasoselective calcium antagonist (Table 1).

**Hemodynamic Effects *in Vivo***

Effects on arterial blood pressure in rats

The antihypertensive potency and the duration of action of clevidipine and its main metabolite H 152/81 \[4-(2′3′-dichlorophenyl)-2,β-dimethyl-1,4-dihedropyridine-3,5-dicarboxylic acid monomethylester\] were determined in anesthetized spontaneously hypertensive (SHR) and in normotensive rats. The following compounds were also tested in SHR: GTN, SNP, felodipine, nicardipine and isradipine. The drugs were infused intravenously at increasing rates for 15 min until blood pressure was reduced by 30%. Antihypertensive potency was defined as the accumulated molar dose of the drug required to lower mean arterial pressure (MAP) by 30% \( \text{ED}_{30} \). At the end of drug infusion, the duration of action was estimated as the time required for MAP to recover to 10% of the control blood pressure. As shown in Table 2, the recovery time following clevidipine is similar to that of
GTN, longer than that of SNP and considerably shorter than that of the calcium antagonists felodipine, isradipine and nicardipine.

The potency of clevidipine in lipid emulsion (the clinically used dosage form) and in 1% Solutol (polyethylene glycol-15-hydroxystearate, BASF) in saline was the same. Its blood pressure lowering potency was higher in spontaneously hypertensive than in normotensive rats. The main metabolite, H152/c4781 (butyroxymethyl methyl 4-(2',3'-dichlorophenyl)-1,4-dihydro-2,6-dimethyl, 3-5-pyridinedicarboxylic acid), did not influence blood pressure at a molar dose 70 times higher than that required for clevidipine to lower arterial blood pressure by 30%. In separate experiments on anesthetized SHR, clevidipine and its two enantiomers were tested. The recovery rate and potency values did not differ between these three compounds. These results demonstrate that clevidipine is an effective and ultrashort-acting antihypertensive agent.

**Effects in anesthetized dogs**

The effects of clevidipine, at increasing i. v. doses, on central hemodynamics of anesthetized beagles were compared with those of SNP (39). Clevdipine reduced mean aortic

<table>
<thead>
<tr>
<th>Compounds</th>
<th>pIC50</th>
<th>IC50 ratio</th>
<th>Selectivity</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil*</td>
<td>6.60</td>
<td>6.46</td>
<td>1.4</td>
<td>7</td>
</tr>
<tr>
<td>Diltiazem*</td>
<td>6.36</td>
<td>5.50</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Nifedipine*</td>
<td>7.62</td>
<td>6.47</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Felodipine*</td>
<td>7.47</td>
<td>5.40</td>
<td>118</td>
<td>6</td>
</tr>
<tr>
<td>Felodipine†</td>
<td>7.61</td>
<td>5.51</td>
<td>126</td>
<td>5</td>
</tr>
<tr>
<td>Clevidipine†</td>
<td>6.37</td>
<td>4.69</td>
<td>48</td>
<td>5</td>
</tr>
</tbody>
</table>

**Note.** pIC50 is the negative logarithm of the molar concentration (IC50), which would reduce by 50% the integrated spontaneous force of the isolated rat portal vein (vascular) and of the peak contractile force of the rat left ventricular papillary muscle (myocardial) residing in the same organ bath. Test compounds were added cumulatively at 10-min intervals; N, number of experiments in each group. *Data from ref. 38; †data from ref. 4.

**TABLE 2. Recovery time and potency of clevidipine and other antihypertensive drugs in rats**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Recovery time (min)</th>
<th>ED30 (nmol/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clevidipine in 20% lipid emulsion — hypertensive rats (SHR)</td>
<td>2.4 ± 0.6</td>
<td>58 ± 9</td>
</tr>
<tr>
<td>Clevidipine in 20% lipid emulsion — normotensive rats</td>
<td>3.0 ± 0.6</td>
<td>316 ± 57*</td>
</tr>
<tr>
<td>Clevidipine in Solutol* saline — SHR</td>
<td>2.4 ± 0.8</td>
<td>59 ± 8</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>0.6 ± 0.2*</td>
<td>184 ± 32*</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>3.9 ± 3.0</td>
<td>2315 ± 2106*</td>
</tr>
<tr>
<td>Felodipine</td>
<td>58.7 ± 26*</td>
<td>26 ± 11*</td>
</tr>
<tr>
<td>Isradipine</td>
<td>43.4 ± 26*</td>
<td>17 ± 2*</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>18.7 ± 8.3*</td>
<td>55 ± 18</td>
</tr>
</tbody>
</table>

**Note.** Mean values ± S.D., for 6 rats per treatment. *p < 0.05 compared to clevidipine in 20% lipid emulsion given to SHR.
blood pressure in a dose-dependent manner by decreasing total peripheral resistance. Cardiac output (CO) increased as a result of an increase in stroke volume, very likely caused by reduced afterload, while heart rate remained unaffected. Thus, despite relaxation of vascular smooth muscle causing a 40% reduction of total peripheral resistance, clevidipine had no direct negative chronotropic or dromotropic effects. This confirms in vitro findings that clevidipine has a high vascular versus myocardial selectivity. The hemodynamic effects of clevidipine and SNP at dosages causing a comparable reduction of MAP are shown in Fig. 2.

The blood pressure reduction caused by clevidipine is due to a profound lowering of total peripheral resistance (TPR) associated with increased cardiac output (CO), while the effect of SNP results mainly from a reduction in CO, which is caused by its venodilatory effect and leads to reduced ventricular filling.

**Miscellaneous effects**

Like other dihydropyridines, clevidipine has a mild natriuretic/diuretic effect when given to rats at a dose, which barely lowers blood pressure (3). At doses well above the therapeutic range, clevidipine inhibits gastrointestinal transport, a property also characteristic of other calcium antagonists. Clevidipine is devoid of effects on the autonomic and central nervous systems and does not interfere with neuromuscular transmission or skeletal muscle function (4,6). Clevidipine has no adverse pharmacological effects on respiratory, liver or endocrine function or on bleeding time.

**Effects on ischemia/reperfusion-induced injury**

 Interruption of organ blood flow causes ischemia, organ malfunction and induces cell death after a critical period of time. Accordingly, early restitution of the arterial blood flow is mandatory to the preservation of organ function. There is, however, ample evi-
dence that restoration of arterial blood flow per se will increase functional and structural injury in the jeopardized tissue. The exact mechanisms underlying this injury are still unclear and have been much debated during the last two decades (1,8,10,42). The initial hyperemic reflow may cause hemorrhage, edema or harmful changes in the inter- and intracellular environments (43). Formation of free radicals, neutrophil and platelet aggregation and calcium overload are among the factors that have been suggested (9,26,50). Calcium antagonists have protective capacity against ischemia/reperfusion injury, but their site of action and protective mechanisms are incompletely understood. The effect of clevidipine on ischemia/reperfusion-related organ injuries has been investigated in a series of experiments.

Free radical-mediated injury

Rats subjected to i.v. infusion of xanthine in combination with xanthine oxidase have a mortality of 90% within 120 min; this effect appears to be related to the generation of oxygen free radicals (29). Clevidipine, at a dose, which reduces MAP by 20%, was studied in this model. Infusion of vehicle or clevidipine was initiated before the administration of xanthine and xanthine oxidase. The 120-min survival rate was 10% in the vehicle group and 50% in rats receiving clevidipine (p < 0.05 vs. vehicle) (23). It was concluded that clevidipine, at a therapeutically relevant dose that reduces MAP by 20%, reduces lethality caused by oxygen free radicals.

Effects on splanchnic and renal ischemia

Ischemia and subsequent reperfusion of the splanchnic vascular bed can cause severe circulatory shock characterized by hemodynamic deterioration with persistently reduced splanchnic blood flow finally leading to death. The possible protective effects of therapeutic and non-therapeutic doses of clevidipine were compared to that of a therapeutic dose of SNP and a vehicle in the rat model of splanchnic ischemia. Blood flow in the superior mesenteric artery was measured before, during and after 60-min occlusion of the celiac and superior mesenteric arteries in anesthetized normotensive rats. Drug administration was started 10 min before the release of the arterial occlusion and lasted 60 min. Blood pressure, heart rate and blood flow were measured for 120 min after the arterial occlusion was released (23). By then, the mesenteric vascular resistance had increased two- to three-fold and mesenteric blood flow recovered to only 20–25% of pre-occlusion value. These variables were similar in rats receiving vehicle, a low dose of clevidipine and SNP. In contrast, the mesenteric blood flow was significantly better maintained following the high dose of clevidipine (23). These results suggest that clevidipine prevents deterioration of the mesenteric circulation during re-oxygenation after mesenteric ischemia.

Ischemic renal failure can occur due to trauma, circulatory shock or certain clinical situations, such as cardiac surgery or renal transplantation. The effects of clevidipine have been studied in a model of renal ischemic failure in anesthetized normotensive rats exposed to unilateral renal artery occlusion for 40 min. Renal function (creatinine clearance) and hemodynamics were evaluated at 30-min intervals prior to, during, and 60 min after renal artery occlusion (49). Vehicle or clevidipine were infused for 60 min, starting at 10 min prior to the release of renal artery occlusion. In both groups, creatinine clearance was markedly reduced, indicating loss of functional nephrons after ischemia/reperfusion. However, despite a similar reduction in creatinine clearance in both groups, urinary volume and sodium excretion were significantly better maintained in rats given clevidi-
pine than in the vehicle group. This suggests that renal tubular reabsorption of sodium and water is partially maintained after reperfusion in the clevidipine group, and that clevidipine, at a therapeutically relevant dose, has salutary effects on renal function after renal artery occlusion and reperfusion.

**Cardioprotective effects**

Interruption of the coronary blood flow causes myocardial ischemia and, after a critical time period, induces myocardial cell death. Accordingly, immediate revascularization is necessary to salvage viable myocardium at risk. Clinically, coronary occlusion is usually triggered by an intracoronary thrombus. Restoration of blood flow can be accomplished by means of thrombolytic agents or coronary interventions like percutaneous coronary angioplasty or coronary artery bypass grafting. However, reperfusion of the ischemic tissue may itself activate pathophysiological processes contributing to the final myocardial injury (10,25).

Calcium antagonists have been shown to decrease myocardial ischemia/reperfusion injury (42). The exact site of action and myocardial protective mechanisms of these drugs are not understood. Before the development of clevidipine, only long-acting calcium antagonists were available for studies on the mechanism of this phenomenon. This made it difficult to distinguish direct effects on the ischemic myocardium from effects on peripheral circulation and on non-jeopardized myocardial tissue. The development of clevidipine created new opportunities to investigate the site of action, mechanisms and time windows of the cardioprotective effects of calcium antagonists. A summary of experiments conducted to elucidate the role of clevidipine in this setting follows.

Pigs were subjected to 45 min of myocardial ischemia through ligation of the left coronary artery followed by 4 h of reperfusion. During the ischemic period before reperfusion, clevidipine or other test compounds or combinations of compounds were administered to the ischemic myocardium by retrograde coronary venous or coronary arterial infusions. The area at risk was determined by infusion of Evans Blue dye into the left atrium, and the infarct size was estimated by triphenyl tetrazolium chloride staining of the myocardial tissue following animal sacrifice (48). In the first set of experiments, clevidipine reduced infarct size by 36% ($p < 0.01$) when given 10 min before the onset of reperfusion. Central hemodynamics or coronary blood flow were not affected. This experiment verified that clevidipine exerts cardioprotective effects against ischemia/reperfusion injury and indicates that this effect relates to local mechanisms within the ischemic myocardium (48).

The effect of clevidipine on the development of myocardial ischemia/reperfusion injury during the early and late phases of ischemia and during early reperfusion was studied in the same experimental model, applying another study protocol. Clevidipine was infused over 5 min into the ischemic myocardium in three groups of pigs starting at 5, 35, or 44 min after the onset of ischemia (13). The infarct size, expressed as a percentage of the myocardial tissue at risk, was significantly smaller in pigs given clevidipine at 5 min (58%; $p < 0.01$) and at 44 min (42%; $p < 0.01$) of ischemia than in pigs receiving clevidipine after 35 min of ischemia (85%). This shows that blockade of calcium influx by clevidipine at the early phase of ischemia and at the time of reperfusion limits infarct size induced by ischemia and reperfusion.

This interpretation is based on the assumption that clevidipine given locally to ischemic myocardium in anesthetized pigs has a very short half-life. When this assumption was
tested using the same protocol (54), the mean blood clearance of clevidipine was calculated to be 0.17 L/min/kg, and the estimated half-life was ~0.5 min. Very low levels of clevidipine were detected in the coronary venous blood in animals subjected to different periods of ischemia, and then during the first two min of reperfusion only. There were no detectable levels in the arterial blood at any time. Blood concentration profiles of clevidipine did not differ with the length of myocardial ischemia. Accordingly, it could be concluded that the systemic concentration of clevidipine does not reach pharmacologically active levels when a dose known to exert cardioprotection is administered into the coronary artery.

Possible mechanisms of myocardial protection by clevidipine

Nitric oxide (NO) is an important regulator of vascular tone; it prevents platelet and leukocyte adherence, and acts as a scavenger of oxygen radicals. An experimental pig model (21) was used to study the effects of clevidipine on preservation of endothelial function and protection against myocardial injury by local NO-mediated mechanisms during late ischemia and early reperfusion. Five groups of pigs were given vehicle, clevidipine, the NO synthesis inhibitor N-monomethyl-L-arginine (L-NMMA), clevidipine in combination with L-NMMA and the NO precursor L-arginine (n = 6) into the left coronary artery during the last 10 min of ischemia and the first 5 min of reperfusion. Data are presented as mean ± S.E.M. Significant differences between the groups and vehicle are shown, ***P < 0.001. Reproduced from ref. 21 with permission from the European Society of Cardiology.
significantly larger in the clevidipine group than in other groups. Therefore, by local administration, clevidipine reduces infarct size during late ischemia and early reperfusion and preserves coronary endothelial function, possibly by maintaining the local bioavailability of NO.

The possible involvement of bradykinin was tested in further investigations of the cardioprotective effects of clevidipine. Bradykinin, a potent endogenous vasodilator, induces endothelial-dependent relaxation via multiple mechanisms, including those involving cyclooxygenase-derived prostanoids and endothelium-derived hyperpolarizing factor (41). Bradykinin contributes to the limitation of infarct size during myocardial ischemia and reperfusion via B2 receptors (30). Four groups of pigs were given vehicle, clevidipine, clevidipine in combination with the bradykinin B2 receptor antagonist HOE 140; icatibant (D-Arg[Hyp3-Thi5-D-Tic7-Oic8]-bradykinin) or clevidipine in combination with HOE, with the nitric oxide donor S-nitroso-N-acetyl-D,L-penicillamine (SNAP) administered into the coronary sinus during the last 10 min of ischemia and the first 5 min of reperfusion (Clev + HOE + SNAP, n = 6). Data are presented as means ± S.E.M. Significant differences from the vehicle group are shown, ***P < 0.001. Reproduced from ref. 22 with permission from Lipincott Williams and Wilkins.

**FIG. 4.** Infarct size as percent of the area at risk after 45 min of ischemia followed by 4 h of reperfusion. The animals were treated with vehicle (n = 10), clevidipine (Clev, n = 10), a combination of clevidipine and bradykinin B2 receptor antagonist HOE 140 (Clev + HOE, n = 6), or a combination of clevidipine and HOE, with the nitric oxide donor S-nitroso-N-acetyl-D,L-penicillamine (SNAP) administered into the coronary sinus during the last 10 min of ischemia and the first 5 min of reperfusion (Clev + HOE + SNAP, n = 6). Data are presented as means ± S.E.M. Significant differences from the vehicle group are shown, ***P < 0.001. Reproduced from ref. 22 with permission from Lipincott Williams and Wilkins.

Summary of the effects of clevidipine on ischemia/reperfusion injury

It can be concluded from this set of experiments that clevidipine protects against ischemia/reperfusion-induced injury of various organs including kidney, splanchnic region and
heart. Experiments performed in the myocardial ischemia/reperfusion model clearly indicates that the mechanisms of the protective action of clevidipine are located within the ischemic tissues, and that they are multifactorial, involving inhibition of free radicals, calcium overload and possibly also comprising bradykinin- and NO-related mechanisms. The evidence suggests that clevidipine has the potential for being clinically beneficial in the treatment of reperfusion-induced injuries, for example in association with cardiac surgery, cardiopulmonary bypass (CPB), percutaneous coronary intervention (PCI), organ transplantation and multi-organ failure.

**TOXICOLOGY**

Clevidipine has been evaluated in a toxicological program in animals and in *in vitro* studies with bacteria, mammalian cells and human blood. In single-dose toxicity studies, the maximal tolerated i.v. dose (MTD) of clevidipine in rodents was determined to be 140 mg/kg in the mouse and 110 mg/kg in rats.

Repeated-dose toxicity studies were performed by exposing rats and dogs to continuous i.v. administration of clevidipine for up to four weeks. In these studies, clevidipine was administered at doses resulting in blood concentrations 4 to 8 times those reached with clevidipine in hypertensive patients. Clevidipine was used as a lipid emulsion, the same formulation as in the clinical trials. The few adverse effects observed in these studies that are possibly related to clevidipine included small biochemical and organ weight deviations. These effects were observed only at the highest doses tested. It was, therefore, concluded that satisfactory safety margins exist in clinical settings for patients receiving therapeutic doses of clevidipine.

A battery of genotoxicity studies of clevidipine included the Ames mutagenicity test, the mouse lymphoma thymidine kinase locus assay, test for chromosome aberrations in human lymphocytes, the lymphocyte transformation test *in vitro* and the mouse micronucleus test *in vivo*. Additionally, fertility and embryofetal studies of clevidipine in the rat and/or rabbits have been performed. Results from *in vitro* and *in vivo* genotoxic studies indicate absence of any clinically relevant mutagenic risk with clevidipine.

Two studies were conducted in dogs and one in rabbits to assess the potential for intravascular, perivascular or skin irritation at administration sites. It was determined that at concentrations and infusion rates far above those intended for clinical use, the infusion of clevidipine caused a slight local vascular irritant effect. These and repeated-dose studies suggest that the clinical administration of clevidipine is likely to be associated with only minimal, if any, irritant effects at the site of injection.

Overall, the results of the toxicology studies indicated that the majority of the clinical, hematological, biochemical as well as morphological effects observed were due to lipid overload, induced by the vehicle. Most of these findings are well-known from previous animal studies performed with agents, like Intralipid®. However, Intralipid® and similar emulsions have been administered to humans for decades. Thus, the vast majority of toxicological findings in animals receiving repeated administration of clevidipine at doses far above those that would be used in clinical practice, have little or no relevance to the use of therapeutic doses of clevidipine in a clinical setting.
CLINICAL STUDIES

Clevidipine has been studied in healthy volunteers, patients with essential hypertension, and in anesthetized or sedated patients during and after cardiac surgery.

Metabolism and Pharmacokinetics

Metabolism

Clevidipine is rapidly hydrolyzed in the blood by cleavage of the ester group resulting in an equivalent formation of the primary metabolite as illustrated in Fig. 5 (18). The rate of hydrolysis of clevidipine is much higher in whole blood than in plasma alone. This suggests that esterases located in the membrane or the cytosol of the red blood cells is most efficient in hydrolyzing clevidipine in blood. The half-life of clevidipine increases with lower blood temperatures. Clevidipine is highly protein-bound in human plasma (~99.7%) (18). No concentration-dependent protein binding of clevidipine has been observed in the dose range studied (18).

The metabolism of clevidipine to the primary inactive metabolite occurs in two steps. Clevidipine is initially metabolized by esterases in the blood to a hemiacetal ester and butyric acid. The unstable hemiacetal ester is chemically converted to the primary and major pharmacologically inactive metabolite of clevidipine found in plasma (Fig. 5). This metabolite is subsequently metabolized to a large extent by glucuronidation, oxidation or decarboxylation before excretion. The pharmacokinetics of the main metabolite, with a terminal half-life of approximately 9 h, differs markedly from clevidipine (15,16). Recovery of approximately 15% of administered radioactivity in feces following intravenous

FIG. 5. Metabolic pathways of clevidipine following administration to humans (L. Fryklund, personal communication).
administration of tritium-labeled clevidipine suggests biliary elimination and/or intestinal secretion of clevidipine and/or its metabolites (15).

Pharmacokinetics

In venous blood collected from healthy volunteers and patients with essential hypertension, there is a lag time of 0.5–1.0 min between the termination of a clevidipine infusion and the start of a rapid decay of clevidipine blood concentrations (15). In contrast, there was no lag time in arterial blood collected from the left radial artery in patients undergoing CABG surgery (53). The presence of an arteriovenous concentration difference was verified when arterial and venous blood samples were collected in healthy volunteers who received clevidipine infusions for up to 24 h (14) (Fig. 6 and Table 3).

Volume of distribution and clearance

The steady state volume of distribution ($V_{ss}$) for clevidipine derived from arterial and venous blood concentrations is listed in Table 3 (14). The mean $V_{ss}$ of clevidipine derived from venous blood is larger than that derived from arterial blood. Irrespective of the blood pool, the volume of distribution for clevidipine is smaller than that reported for other dihydropyridine calcium antagonists, such as felodipine (45). The blood clearance of clevidipine has been determined by non-compartmental and compartmental analysis of individual data, as well as by population approach (Table 3). These distinct methods provided similar results in comparative study groups. It is noteworthy that blood clearance of clevidipine during hypothermic CPB is only half of the value found during normothermia.

As already described, arterial blood concentrations are approximately twice as high as those in venous blood at steady state (Fig. 6). Accordingly, mean blood clearance values derived from venous blood are approximately twice those obtained from arterial blood concentrations (Table 3).
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Population</th>
<th>Model</th>
<th>Dose (nmol/min/kg)</th>
<th>Duration (h)</th>
<th>Sample site</th>
<th>CL (L/min/kg)</th>
<th>$V_c$ (L/kg)</th>
<th>$V_{ss}$ (L/kg)</th>
<th>$k_{10}$ (min⁻¹)</th>
<th>Half life ($t_{1/2}$) (min)</th>
<th>Fract constant (C) (%)</th>
<th>AUC₁ (%)</th>
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<td>—</td>
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**Note.** Pop, population approach; N.C., non compartmental analysis; 2-C, two-compartment model; 3-C, three-compartment model; CPB, cardiopulmonary bypass.
Half-life and decrement times

As shown in Table 3, the half-lives associated with the exponential phases of the blood concentration vs. time curve vary slightly in different studies (12,14). However, characterizing pharmacokinetics of a drug with disposition models containing two or three exponential phases with different half-lives is sometimes done by arbitrary judgments. The important phases in describing the pharmacokinetic properties of clevidipine are those immediately after cessation of the infusion, since the initial rapid post-infusion decline in clevidipine levels is primarily related to elimination (15). Thus, use of decremental times rather than different half-lives is more appropriate for describing the pharmacokinetics of clevidipine. In order to illustrate the initial rapid decline, the time to reach 50% and 90% post-infusion decline in concentrations of clevidipine and nicardipine following various infusion times are shown in Fig. 7 (12,14,27). The simulations showed that the 50% post-infusion decline (context-sensitive half-time) of clevidipine is less than 1 min regardless of the duration of the infusion. The time to reach a 90% decline is approximately 5 min following clinically relevant infusion times. The corresponding times for nicardipine changed with the duration of the infusion. The reason for this difference is that the initial rapid post-infusion decline in clevidipine blood levels is primarily related to elimination, whereas the corresponding decline for nicardipine is due to distribution.

Influence of dose and duration of infusion

There is a linear relationship between the dose and the steady state blood concentrations of clevidipine in healthy volunteers receiving clevidipine at rates between 1.5 and 48 nmol/min/kg and in patients with essential hypertension receiving between 0.4–12 nmol/min/kg (14,16,46). Furthermore, the pharmacokinetic parameters of clevidipine are essentially unaffected by the duration of the infusion. Results obtained during infusion times from 10 min to 24 h, are comparable (14) (Table 3).
Pharmacodynamic Effects in Clinical Trials

Studies in healthy volunteers

In three studies with healthy volunteers (14–16), clevidipine was administered intravenously as a continuous infusion at different rates for different time periods. A dose-dependent effect on blood pressure was fully established within an average of 2 min after initiation of clevidipine infusion (14). The dose and duration of infusion did not significantly impact the time of recovery of blood pressure to pre-drug values after the end of infusion (24). In these conscious individuals, there was a concomitant, dose-dependent and modest increase in heart rate. Clevidipine was considered well tolerated up to a dose of 16 µg/kg/min. At the highest dose of 22 µg/kg/min, MAP was reduced by 10%. At this dose, the heart rate had reached the predetermined safety endpoint of 120 bpm, the reason to stop further dose escalation in accordance with the protocol (16).

Studies in patients with essential hypertension

Two studies with clevidipine were performed in conscious patients with essential hypertension (4,7). In the first study (5), clevidipine was titrated to obtain a predetermined effect on MAP, with the infusion being stopped when the MAP was reduced by 15% from baseline. As illustrated in Fig. 8, there was a rapid decline of the clevidipine effect after discontinuation of the infusion, with blood pressure returning to baseline within minutes. These patients were on chronic oral treatment with β-adrenoceptor antagonists and demonstrated no change in HR.

In the second study (46), a placebo-controlled trial, clevidipine was slowly titrated to predetermined dose rates in 20 patients from whom antihypertensive treatment had been withdrawn for two weeks. Clevidipine caused dose-dependent reductions in arterial blood pressure with a maximum reduction of approximately 30% at the highest infusion rate. These patients, who were off concomitant beta blockade, had a modest increase in HR. The effects of clevidipine rapidly vanished after the end of drug infusion.

FIG. 8. Effect of increasing doses of clevidipine given to reduce mean arterial blood pressure (MAP) 5, 10, and 15% from basal MAP (125 mm Hg) in one patient with essential hypertension. Data from ref. 5. Note the rapid return of MAP to control after end of infusion.
Studies in patients undergoing cardiac surgery

The clinical efficacy and safety of clevidipine in anesthetized patients undergoing cardiac surgery have been investigated in five studies. Three of these studies were conducted postoperatively (7,31,44) and two were performed perioperatively (2,53).

Postoperative studies in cardiac surgery patients

A placebo-controlled parallel-group dose-finding study was performed in 91 anesthetized patients with a MAP exceeding 90 mm Hg (7). Clevidipine was given for a minimum of 10 min at six different dose rates. As shown in Fig. 9, the administration of clevidipine resulted in a dose-dependent reduction in MAP with a maximum reduction of 38%. There was no increase in heart rate in these anesthetized patients, probably due to attenuation of the baroreflex sensitivity during anesthesia (33).

In another study (31) evaluating central and coronary hemodynamics, clevidipine was titrated in 8 anesthetized, normotensive patients post-CABG in the intensive care unit. Dose-dependent reductions in MAP were achieved, mainly due to a decrease in SVR. Cardiac filling pressures were not influenced, reflecting the fact that clevidipine does not cause venous dilation. Afterload reduction was associated with a dose-dependent increase in stroke volume (Fig. 10). Heart rate was not influenced in these patients.

Each patient had a four-thermistor catheter inserted via the jugular vein and positioned for coronary blood flow determinations and blood sampling. High doses of clevidipine caused coronary vasodilatation as indicated by a reduction in myocardial oxygen extraction. There were no adverse effects on myocardial lactate metabolism, indicating that the coronary vasodilatation did not result in shunting of blood from ischemic areas, i.e., coronary steal (31).

The hemodynamic effects of clevidipine were compared with those of SNP, using a crossover study design (31). Patients in need of blood pressure control after CABG (n = 13) were recruited. Therapy was initiated with SNP and a hemodynamic evaluation was performed when blood pressure control was satisfactory. Subsequently, the SNP infusion was discontinued and replaced by clevidipine infusion. The dose was adjusted to

![Figure 9](image_url)
control MAP at the same level (70–80 mm Hg) as reached with SNP. Repeated hemodynamic evaluation revealed that clevidipine had a more pronounced effect on SVR than SNP. With clevidipine, there was no reduction in central venous pressure or pulmonary capillary wedge pressure and stroke volume was higher than with SNP. HR was statistically significantly lower during clevidipine than with SNP, although the difference in actual number of beats per minute was small (Fig. 11).

In the third study in post-cardiac surgical patients, Powroznyc et al. (44) evaluated blood pressure control with clevidipine and SNP in hypertensive patients (MAP = 90 mm Hg) in a parallel group (n = 15 in each group), double-blind comparison after elective CABG. Blood pressure was equally well controlled with both drugs, but heart rate remained significantly higher in the SNP group.

In summary, these studies in post-cardiac surgical patients reveal that clevidipine rapidly reduces blood pressure in a dose-dependent manner without affecting cardiac filling pressures or heart rate. This effect contrasts with that of SNP, which besides exerting its effects on blood pressure, also reduces cardiac filling pressure and increases heart rate in anesthetized patients after cardiac surgery.
FIG. 11. Hemodynamic effects of shifting antihypertensive therapy from sodium nitroprusside (SNP 1) to clevidipine for 10 min and then back to sodium nitroprusside (SNP 2) in 8 anesthetized cardiac surgical patients requiring pharmacological treatment for blood pressure control during and after cardiac surgery. Mean ± S.E.M., *p < 0.05 from SNP. PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; CVP, central venous pressure. Data from ref. 31.
**Perioperative studies in cardiac surgery patients**

The dose of clevidipine required to control blood pressure before and during cardiopulmonary bypass (CPB) was compared in 8 patients during CABG surgery (53). The infusion rate of clevidipine needed to reduce MAP to the required level during the pre-bypass stage (normothermic) was two times the infusion rate required during bypass (hypothermic) conditions. The lower infusion rate during CPB is likely to be secondary to the decreased blood clearance of clevidipine during hypothermia and blood dilution (see the Pharmacokinetics and Metabolism section of this review).

Clevidipine was shown to be significantly more effective than placebo in the perioperative reduction of blood pressure in a double-blind study of 60 patients undergoing CABG (2). The MAP reduction within 10 min after start of drug infusion with clevidipine was 28.2 mm Hg, compared to 10.5 mm Hg with placebo \( p < 0.001 \). Control of MAP was estimated by the AUC relating MAP outside a predetermined blood pressure level vs. time. During the first 4 h, blood pressure was significantly better controlled with clevidipine than with placebo, AUC during clevidipine being only 63% of that during placebo administration. Bailout with GTN to protect against too high blood pressure levels while on drug was performed for only 4/29 (14%) of patients in the clevidipine treatment group, compared with 27/31 (87%) of patients in the placebo group. In addition, the number of pharmacological or mechanical interventions needed to control blood pressure either upwards or downwards were higher for patients in the placebo group than in patients receiving clevidipine.

**Adverse events**

Many of the patients evaluated in the cardiac surgery studies described here, including those on placebo, were reported as having adverse events. The most frequently reported adverse events were atrial tachyarrhythmia, and overall the most frequently affected body systems included the cardiovascular, gastrointestinal and respiratory functions. These findings probably reflect the complex situation in patients undergoing heart surgery, since no clear differences in the incidence of adverse events were observed for patients on placebo vs. patients on clevidipine. In the placebo controlled study including 60 patients (2), treatment with clevidipine or placebo was discontinued due to adverse events in 13 cases (hypotension \( n = 8 \); hypertension \( n = 4 \); bleeding \( n = 1 \); bradycardia \( n = 1 \)). All patients recovered completely. Twenty-seven patients of the 212 patients in the program undergoing cardiac surgery experienced a total of 53 serious adverse events (2,7,31,35,53) but only one of these events (7) was considered as possibly related to clevidipine.

**Time to effect, offset of effect and PK/PD relation**

When time to onset of hemodynamic effect(s) was determined in healthy volunteers, it was found that the arterial blood concentrations of clevidipine had reached steady state within 2 min after start of drug infusion. There was a close relation between blood concentration and observed changes in mean arterial blood pressure and in heart rate. However, there was a very brief delay between the change in the arterial blood concentrations and
the hemodynamic response (14). As illustrated in Fig. 12, the effects of clevidipine can be rapidly titrated to a desired blood pressure level.

CONCLUSIONS

Clevidipine is a new vasoselective, short-acting dihydropyridine calcium antagonist with pharmacological and pharmacokinetic properties well suited for acute blood pressure control requiring rapid onset and offset of action. The therapeutic effects of clevidipine have been demonstrated in clinical situations such as cardiac surgery and post-operative intensive care after coronary bypass procedures. Clevidipine is likely to be similarly effective in other clinical situations requiring rapidly tailored blood pressure control. In animal models, clevidipine exerts organ protective properties in association with ischemia/reperfusion. These properties may provide added benefit to patients treated with clevidipine, particularly since ischemia/reperfusion frequently occurs in the same clinical settings as those in which acute blood pressure control may be useful. Further clinical studies in this area are warranted. Based on results from the ongoing clinical program clevidipine has a rapid onset dose-dependent blood pressure lowering effect, along with a rapid offset of effect and favorable hemodynamic properties. These results suggest that clevidipine has suitable attributes to become a useful novel therapeutic agent for use in acute care situations requiring rapid blood pressure control.

REFERENCES


