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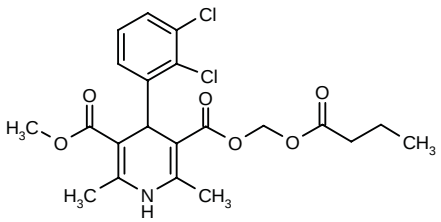
Clevidipine

Prop INN

Treatment of Hypertension
Calcium Channel Blocker

Clevelox™

(±)-4-(2,3-Dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid butyryloxymethyl methyl diester



$C_{21}H_{23}Cl_2NO_6$

Mol wt: 456.327

CAS: 167221-71-8

EN: 226911

Abstract

A sudden increase in systemic blood pressure is a common event after cardiac surgery. These acute elevations in blood pressure do not necessarily meet the true criteria for clinical hypertension and no currently available agent has been found to be optimal for the management of postoperative hypertension. Available treatments include nitroso-vasodilators, which are short-acting but not vascular-selective vasodilators. These agents are also associated with tachyphylaxis, reflex tachycardia and rebound hypertension. Other treatment options include dihydropyridine calcium channel blockers. However, those agents available to date have a relatively long plasma half-life, resulting in unwanted prolonged effects. Clevidipine is a novel, arterial-specific, ultra-short-acting vasodilator of the dihydropyridine class of calcium channel blocker. The agent was developed to specifically reduce and control acute increases in arterial pressure in the cardiac surgical setting. It is cleared rapidly and has a small volume of distribution, resulting in a short plasma half-life and a short duration of action. Clevidipine has shown cardioprotective and blood pressure-lowering effects in animal models and the agent was safe and endowed with antihypertensive efficacy in the clinic. Clevidipine is presently undergoing phase III development for the treatment of perioperative hypertension.

Synthesis

Clevidipine is prepared by esterification of 4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid monomethyl ester (I) with chloromethyl butyrate (II) by means of $NaHCO_3$ in DMF at 80 °C (1) or refluxing acetonitrile (2). Scheme 1.

Introduction

The sudden increase in systemic blood pressure commonly observed after cardiac surgery is a significant clinical problem requiring management. The increase in blood pressure can cause an increase in myocardial work and is poorly tolerated by hearts with systolic dysfunction. Acute increases in afterload to the left ventricle could result in reductions in stroke volume, increases in left ventricular filling pressure and pulmonary congestion. In addition, increases in blood pressure may result in subendocardial ischemia, bleeding from surgical sites and cerebrovascular hemorrhage (1-6).

Elevations in blood pressure following cardiac surgery do not necessarily meet the true criteria for clinical hypertension and no currently available agent has been found to be optimal. Nitroso-vasodilators such as sodium nitroprusside and nitroglycerin are short-acting vasodilators which are used clinically to manage postoperative hypertension. However, they are associated with tachyphylaxis, reflex tachycardia and rebound hypertension and they are not vascular-selective and can result in venodilatation. Hydralazine and fenoldopam, a dopamine D1 agonist, are also treatment options, although like the nitroso-vasodilators, they are associated with reflex tachycardia. Other agents for the treatment of acute postoperative hypertension include calcium channel blockers such as those of the dihydropyridine class. However, compounds such as nifedipine, nicardipine and isradipine have a relatively long plasma half-life resulting in unwanted prolonged effects (7-16). Thus, the search for arterial-specific vasodilators with a rapid onset and offset of action and a low incidence of side effects continues.

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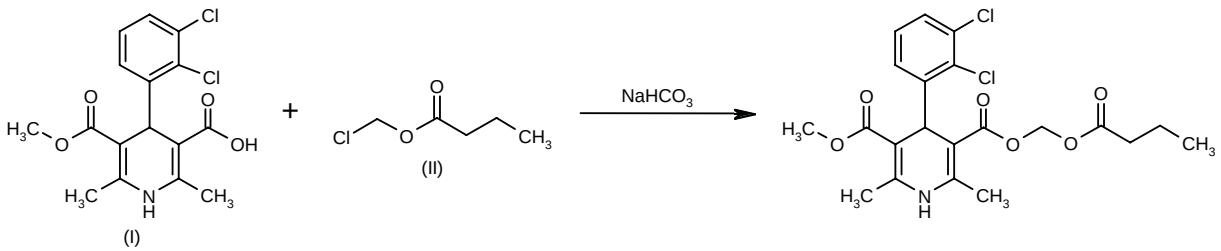
Scheme 1: Synthesis of Clevidipine



Clevidipine (Clevelox™) is a novel, arterial-specific, ultra-short-acting vasodilator of the dihydropyridine class of calcium channel blockers. The agent was developed to specifically reduce and control acute increases in arterial pressure in the cardiac surgical setting. Clevidipine is cleared rapidly and has a small volume of distribution, resulting in a short plasma half-life and short duration of action. Clevidipine was chosen for further development as a treatment for perioperative hypertension.

Pharmacological Actions

The vasodilating effects of clevidipine were examined in an *in vitro* study using human internal mammary artery. The addition of clevidipine to segments with or without intact endothelium and precontracted with the thromboxane A_2 analogue U-46619 (0.01 μM) was found to completely reverse contractions (EC_{50} = 3.88 ± 0.84 μM); nitroglycerin was also effective (EC_{50} = 0.048 ± 2.76 μM). Thus, clevidipine was a potent, endothelium-independent vasodilator in this model (17).

An *in vitro* study using isolated guinea pig ventricular myocytes examined the blocking effects of clevidipine on the L-type Ca^{2+} current. When cells were clamped at –80 mV, clevidipine (10 nM) decrease I_{Ca} by about 30%. However, if cells were clamped at –40 mV, the agent blocked I_{Ca} by more than 50%. Depolarizing the membrane to –40 mV was found to increase recovery time (τ_{off}) of clevidipine-induced inhibition of I_{Ca} more than 3-fold and markedly reduced the dissociation constant (K_D) from 65 ± 3 nM at a holding potential of –80 mV to 9.0 ± 0.8 nM. Thus, clevidipine like other dihydropyridines, binds to the L-type Ca^{2+} channel in a voltage-dependent manner, exhibiting increased affinity and enhanced inhibitory activity at depolarized holding potentials (18).

Clevidipine showed selectivity for inotropic as opposed to chronotropic effects in an *in vitro* study using perfused rat hearts. Treatment with the agent (1 nM-1 μM) did not affect spontaneous heart rate or atrioventricular conduction. In contrast, both nifedipine and isradipine induced a concentration-dependent reduction in these parameters. A concentration-dependent suppression of cardiac contractility was observed with all compounds. Administration of clevidipine or nifedipine resulted in a proportionate decrease in left ventricular dP/dt_{max} that was greater than that for heart rate. This resulted in a high inotropic as opposed to chronotropic selectivity. In contrast, administration of isradipine decreased both heart rate and contractility in a concentration-dependent manner (19).

A study using pigs subjected to 45 min of myocardial ischemia (*i.e.*, occlusion of the left anterior descending coronary artery [LAD]) followed by reperfusion for 4 h demonstrated the cardioprotective effects of clevidipine (0.3 nmol/kg/min via retrograde venous infusion over 30 min starting 10 min before reperfusion). The infarct size (expressed as a percentage of the area at risk) was significantly reduced in animals receiving clevidipine (51 ± 9.2% *vs.* 80 ± 9.2%). The agent had no effect on heart rate, left ventricular systolic and end-diastolic pressure, dP/dt_{max} or mean arterial blood pressure (20). The cardioprotective effects of clevidipine were shown to be time-dependent in another study using a similar protocol. In this study, administration of clevidipine (0.3 nmol/kg/min over 5 min starting 5, 35 or 44 min following ischemia onset) significantly reduced infarct size when administered after 5 (58 ± 17% of area at risk) and 44 (42 ± 6%) min of ischemia as compared to animals administered the agent after 35 min of ischemia (85 ± 4%). Results suggest that clevidipine exerts cardioprotective effects when administered during the early phase of ischemia and at the time of reperfusion in this model (21).

Results from other studies in pigs subjected to 45 min of LAD ligation followed by 4 h of reperfusion suggested that the reduction in myocardial reperfusion injury produced by clevidipine is mediated via nitric oxide (NO)- and bradykinin-related mechanisms. Administration of clevidipine alone (0.3 nmol/kg/min during the last 10 min of ischemia and the first 5 min of reperfusion) significantly reduced infarct size compared to controls. Coadministration of clevidipine with Hoe-140 (0.01 μg/kg/min), a bradykinin B_2 receptor antagonist, or L-NMMA (0.2 mg/kg), an NO synthase inhibitor, abolished the cardioprotective effects of clevidipine. Moreover, addition of the NO donor SNAP (0.016 μmol/min) or the NO precursor L-arginine (2 mg/kg) restored clevidipine-induced cardioprotection (22, 23).

Clevidipine had no effect on the potency of the anesthetic isoflurane in rats and dogs. A minimal but significant reduction in minimum alveolar concentration (MAC) of isoflurane was obserrved in rats anesthetized with isoflurane and given clevidipine (20 or 40 nmol/kg/min) compared to controls. However, MAC_{awake} and duration of sleep were unaffected in isoflurane-anesthetized dogs treated with the agent (6 nmol/kg/min) (24).

In addition to its cardioprotective and vasodilating effects, clevidipine was demonstrated to have potent natriuretic effects in a study involving administration at a dose of 5 nmol/kg/min i.v. for 60 min starting 10 min before reperfusion to anesthetized rats subjected to occlusion of the left renal artery for 40 min followed by reperfusion. In normal anesthetized rats not subjected to ischemia/reperfusion, infusion of either clevidipine or fenoldopam significantly increased urine flow, urinary sodium excretion and fractional excretion of sodium; clevidipine infusion also significantly reduced mean blood pressure. In rats with ischemia/reperfusion-induced acute renal failure, infusion of clevidipine improved tubular function with significant attenuation of the reductions in sodium and urine flow and restoration of urine flow and urinary sodium excretion to basal levels. On the other hand, tubular function was further deteriorated in animals treated with fenoldopam. Neither treatment improved filtration fraction. Thus, although both agents exerted natriuretic effects in normal rats, only clevidipine preserved renal function in rats with acute renal failure (25).

Pharmacokinetics

A capillary gas chromatography-mass spectrometry method with negative ion chemical ionization was described to quantitatively determine clevidipine concentrations in whole blood. Liquid chromatography and fluorescence detection were described to determine the primary metabolite, methyl 4-(2',3'-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (M1; H-152/81). Due to its rapid metabolism, clevidipine was stabilized in blood using sodium dodecyl sulfate to prevent ester hydrolysis. The limit of quantification was 0.5 nmol/l blood for clevidipine and 50 nmol/l blood for M1 (26).

The conditions for fast separation of the enantiomers of clevidipine by SFC using a 50 x 4.6 nm ID short Chiralpak AD column with 2-propanol-modified carbon dioxide as the mobile phase were presented. With this method, high-throughput analysis of the parent drug and its enantiomeric composition is possible (27). Another study examined the influence of different mobile-phase parameters such as type and concentration of organic modifier, mobile-phase pH and column temperature, to determine how enantioselective retention of clevidipine can be controlled on Chiral-AGP. Optimized chromatographic methods were described to determine less than 0.1% of an enantiomer impurity in (*R*)- and (*S*)-clevidipine (28).

The pharmacokinetics of clevidipine and its primary metabolite H-152/81 were examined in rats, rabbits and dogs. Clevidipine was administered as an infusion at doses of 20, 67 and 200 nmol/min/kg over 120 min to rats, 6, 18 and 54 nmol/kg/min over 45 min to dogs, and 54 and 83 nmol/kg/min over 30 min to rabbits. The metabolite was administered as an i.v. bolus dose (2.25 µmol/kg) over 1 min to rats. Clevidipine was shown to be rapidly cleared (0.331, 0.165 and 0.291 l/min/kg in rats, dogs and rabbits, respectively) with a relatively small volume of distribution (0.42, 0.21 and 0.14 l/kg, respectively) in all species. This resulted in an extremely short half-life of 12, 20 and 22 s in rabbits, rats and dogs, respectively. Dose rate, gender or weight had no significant influence on the pharmacokinetics of clevidipine in rats. The major metabolite was found to be a high-clearance compound in dogs and a low-clearance compound in rats. In rats, gender was discovered to significantly affect the clearance (0.022 l/h/kg in males *vs.* 0.013 l/h/kg in females) and terminal half-life (12.8 h in males *vs.* 18.9 h in females) of the metabolite. In dogs the mean maximum reduction in arterial blood pressure (E_{max}) was reported to be 38 ± 12% (EC_{50} = 85 ± 46 nM). The half-life value obtained in dogs to reach equilibrium between the central and the effect compartment was 47 ± 49 s (29).

The *in vitro* hydrolysis rate and protein binding of clevidipine were examined in blood from rats, dogs and human volunteers. The *in vitro* half-life of the agent was 0.6, 15.7 and 5.8 min, respectively; this value was about 9 min in human blood from volunteers who were pseudocholinesterase-deficient. Hydrolysis rates were found to be higher in blood and red blood cells (RBCs) as compared to plasma, suggesting that esterases found in RBCs are more essential to the metabolism of clevidipine. In all species, the protein binding of clevidipine and its enantiomers in plasma was > 99.5%. In humans, stereospecific protein binding of the enantiomers was observed (free fraction = 0.43% and 0.32% for the (*S*)- and (*R*)-enantiomer, respectively) (30).

The pharmacokinetics of locally administered clevidipine (0.3 nmol/kg/min infused over 5 min) into the coronary circulation were determined in normal pigs and pigs subjected to LAD ligation (15, 35 or 45 min) followed by 60 min of reperfusion. Steady-state levels of clevidipine in the coronary venous blood of normal pigs were about 30 nM during infusion, with a decrease to about 1 nM (*i.e.*, the detection limit) within 3 min. The mean blood clearance and estimated half-life values were 0.17 l/min/kg and 0.5 min, respectively. In animals subjected to ischemia, no clevidipine could be detected at any time in arterial blood and only small amounts were noted during the first 2 min of reperfusion in coronary venous blood. The duration of ischemia did not influence blood clevidipine levels, indicating that it does not affect cardiac metabolism of the agent (31).

Three studies have reported the pharmacokinetics of clevidipine in healthy volunteers. In one study, 8 healthy male volunteers were administered clevidipine (1030 nmol/min by 1-h i.v. infusion) together with a tracer dose

of [^{3}H]-clevidipine. Mean blood clearance, volume of distribution at steady state, initial half-life and terminal half-life values were 0.14 ± 0.03 l/min/kg, 0.6 ± 0.1 l/kg, 1.6 ± 0.3 min and 15 ± 5 min, respectively. Peak plasma levels of the major metabolite were reached at 2.2 ± 1.3 min postinfusion and the mean terminal half-life of the metabolite and mean recovery of radioactivity were 9.5 ± 0.8 h and 83 ± 3%, respectively. Clevidipine had a short duration of action, with the changes in heart rate (increase from 59 ± 6 to 82 ± 9 beats/min) and mean arterial blood pressure (decrease from 87 ± 8 to 77 ± 6 mmHg) seen during clevidipine infusion returning to baseline values within 15 min postinfusion (32).

Another pharmacokinetic study involving 25 subjects (of whom 21 were included twice) reported a linear relationship between clevidipine blood concentrations and dose (0.12-48 nmol/min/kg by i.v. bolus). The median clearance value for clevidipine determined by noncompartmental analysis was 0.125 l/min/kg. Population mean clearance and volume of distribution at steady state were 0.121 l/min/kg and 0.56 l/kg, respectively. The initial and terminal half-life values were 1.8 and 9.5 min, respectively. The agent was well tolerated, with flush and headache the most common adverse events reported. Mean arterial blood pressure was decreased by 10% at the highest clevidipine dose (33).

The pharmacokinetics of clevidipine administered as a short (7 nmol/kg/min over 20 min) and long (2 or 7 nmol/kg/min for 24 h) i.v. infusion were examined in 24 healthy male volunteers. The pharmacokinetics obtained were not influenced by infusion duration and were found to fit a triexponential disposition model. Mean arterial blood clearance and mean volume of distribution at steady state were 0.069 l/kg/min and 0.19 l/kg, respectively. Mean arterial blood concentrations reached steady state within 2 min of infusion and were approximately twice as high as steady-state venous blood concentrations (34).

A study involving 20 patients with essential hypertension administered racemic clevidipine (20% lipid emulsion formulation; 0.035, 0.17, 0.5 or 1 mg/ml by continuous i.v. infusion starting with a 120-min titration phase followed by 4 x 30-min titration steps after which the final dose was continued for another 120 min) characterized the individual pharmacokinetics of the (–)-(*R*)- and (+)-(*S*)-enantiomers of clevidipine, with only minor differences detected. Both enantiomers were found to be high-clearance compounds with comparable blood clearance values. The mean blood clearance for the (–)-(*R*)- and (+)-(*S*)-enantiomers was 0.103 and 0.096 l/min/kg and the volume of distribution at steady state was 0.39 and 0.54 l/kg, respectively. The context-sensitive half-life for each was about 2 min. Concentrations of the (–)-(*R*)- and (+)-(*S*)-enantiomers decreased by 90% at 8 and 1 min, respectively. The differences in volume of distribution of the enantiomers were suggested to be to differential protein binding. It was concluded that the use of a single enantiomer rather than racemic clevidipine has no significant clinical advantage (35).

The pharmacokinetics of clevidipine (0.18, 0.91, 274 and 5.48 μg/kg/min by i.v. infusion starting with a 120-min titration phase followed by a fixed-dose phase of 120 min) were examined in a randomized, placebo-controlled, single-blind, 5-arm, 3-way crossover study involving 20 patients with mild to moderate hypertension. The agent was well tolerated, only 1 patient being excluded at 2.74 μg/kg/min for adverse events (headache, ventricular extrasystoles, nausea and vomiting). Blood concentrations and dose were found to be linearly related. A high clearance of 0.105 l/min/kg and low volume of distribution at steady state of 0.51 l/kg were reported. The initial and terminal half-life values were 2.2 and 16.8 min, respectively. Dose-dependent reductions in blood pressure were observed. The blood concentration and dose rate resulting in half-maximal effect were approximately 25 nM and 1.5 μg/kg/min, respectively (36).

A study conducted in 17 patients undergoing mild hypothermic cardiopulmonary bypass examined the pharmacokinetics of clevidipine (0.5 mg/ml by i.v. infusion as a 20% lipid emulsion) given before or during surgery. Concentrations of clevidipine in mixed venous and arterial blood were almost the same, indicating that pulmonary metabolism of the agent is insignificant. A high total blood clearance of 0.055 l/min/kg was obtained. Clearance of the agent was significantly decreased to 0.03 l/min/kg in patients administered clevidipine during surgery, possibly due to the decrease in body temperature. The infusion rate required to control arterial pressure before and during surgery was 2.2 ± 0.9 and 1.3 ± 0.4 μg/kg/min, respectively (37).

A randomized study in 91 patients who had undergone cardiac surgery examined the pharmacokinetics of clevidipine (0.05, 0.18, 0.32, 1.37, 3.19 or 9.58 μg/kg/min postoperatively as a 22-min titration phase followed by a 100-min fixed-rate infusion; those patients requiring further antihypertensive treatment received subsequent infusions for up to 12 h). Data were presented from 85 patients. A 3-compartment model best fit the pharmacokinetic data. Clearance and volume of distribution were 4.3 l/min and 32.4 l, respectively. A half-life of 0.6 min was obtained for the early phase of drug disposition and the context-sensitive half-life was less than 2 min for up to 12 h of administration. Treatment with doses of 1.37 μg/kg/min or greater significantly reduced mean arterial blood pressure and systemic vascular resistance. The plasma concentrations associated with a 50% probability of a 10% or greater and 20% or greater reduction in mean arterial blood pressure (C_{50}) for clevidipine were 9.7 and 26.3 μg/l, respectively. No alterations in heart rate, central venous pressure, pulmonary artery occlusion pressure or cardiac index were observed with treatment (38).

Clinical Studies

The safety and efficacy of clevidipine (0.375, 0.75, 1.5 and 3 μg/kg/min) administered after coronary artery bypass grafting (CABG) were examined in a trial conducted in 18 patients. Five patients did not complete

the study due to postoperative bleeding requiring reoperation, postoperative normotension or malposition of coronary sinus catheter. The study included a hypertensive phase (n=13) in which the effects of clevidipine (2.27 ± 0.65 μg/kg/min) were compared to sodium nitroprusside (1.14 ± 0.21 and 0.68 ± 0.04 μg/kg/min before and after clevidipine infusion, respectively) in the control of postoperative hypertension, and a normotensive phase (n=9) in which a clevidipine (0.375, 0.75, 1.5 and 3 μg/kg/min) dose-response curve was determined. In the hypertensive phase when patients achieved the target mean arterial pressure of 75 mmHg, systemic vascular resistance and heart rate were lower, while cardiac preload, stroke volume and pulmonary vascular resistance were higher in patients treated with clevidipine as compared to sodium nitroprusside; no differences in myocardial lactate metabolism or oxygen extraction were observed for the agents. In the normotensive phase of the study, dose-dependent reductions in mean arterial pressure, systemic vascular resistance and pulmonary vascular resistance of –19, –27 and –15%, respectively, were observed. A dose-dependent increase in stroke volume of 10% was also reported; no reflex increase in heart rate or alterations in cardiac preload were noted. Treatment with clevidipine reduced myocardial oxygen extraction from 54% to 45%, indicating a direct coronary vasodilating effect. Blood clearance, volume of distribution at steady state, initial half-life and terminal half-life values were 0.05 l/min/kg, 0.081 l/kg, < 1 min and 4 min, respectively (39).

A randomized, double-blind, double-dummy study conducted in 30 patients who underwent elective coronary bypass surgery compared the efficacy of clevidipine with sodium nitroprusside in controlling hypertension after surgery. The mean doses of clevidipine and sodium nitroprusside to control arterial pressure used in the trial were 0.76 ± 0.83 and 0.58 ± 0.54 μg/kg/min, respectively. No significant difference was observed for clevidipine and sodium nitroprusside in mean arterial pressure AUC values (106 ± 25 and 101 ± 28 mmHg·min/h, respectively), indicating similar efficacy in controlling blood pressure. However, a lesser increase in heart rate was observed in clevidipine-treated patients as compared to those receiving sodium nitroprusside. Moreover, a significant decrease in stroke volume, central venous pressure and pulmonary artery pressure were observed in patients treated with sodium nitroprusside, but these effects were not seen in clevidipine-treated patients. Thus, both agents exhibited similar efficacy in controlling mean arterial pressure postoperatively, although hemodynamic changes including tachycardia were less in the group receiving clevidipine (40).

Clevidipine is in phase III clinical development as a treatment for hypertension associated with cardiac surgery (41, 42).

Sources

AstraZeneca R&D (SE); licensed worldwide (except Japan) to The Medicines Co. (US).

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