Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2025.61.009563

Clinical Pharmacology of Clevidipine

Gian Maria Pacifici*

Professor of Pharmacology, Via Sant' Andrea 3256127 Pisa, Italy

***Corresponding author:** Gian Maria Pacifici, Professor of Pharmacology, Via Sant' Andrea 3256127 Pisa, Italy

ARTICLE INFO

Received: March 24, 2025

Published: April 01, 2025

Citation: Gian Maria Pacifici. Clinical Pharmacology of Clevidipine. Biomed J Sci & Tech Res 61(2)-2025. BJSTR. MS.ID.009563.

ABSTRACT

Clevidipine is a third generation dihydropyridine and is a multiple Ca2+ channel blocker approved for clinical use and clevidipine is used for intravenous management of hypertension. Clevidipine has been found efficacy and safe in hypertensive patients but induces some adverse-effects which occur in a limited rate. Six studies have been reported on treatment of hypertensive patients with clevidipine and three studies have been reported on clinical trials conducted with clevidipine in hypertensive patients. Clevidipine is metabolized into the inactive metabolite H152/81. The pharmacokinetics of clevidipine have been studied in hypertensive patients following clevidipine infusion at the rate of 2 to 16 mg/h. Clevidipine is rapidly eliminated and the elimination of clevidipine consists in two phases. Clevidipine peak concentration, the area under the concentration-time curve, and the concentration at steady-state increase with the dose whereas the total body clearance and the elimination half-life of the initial and terminal phases are not dose related. The half-life of the initial phase is approximately 3.5 minutes and that of the terminal phase is approximately 33 minutes. Clevidipine consists in two enantiomers and the elimination half-life of the initial phase is approximately 2 minutes for both enantiomers whereas the elimination half-life of the terminal phase is approximately 8 minutes for (-)-R-clevidipine and 11 minutes for (+)-S-clevidipine. The aim of this study is to review clevidipine efficacy and safely, treatment of hypertensive patients with clevidipine, adverse-effects induced by clevidipine, trials conducted with clevidipine in hypertensive patients, the metabolism of clevidipine, and the pharmacokinetics of clevidipine.

Keywords: Adverse-Effects; Clevidipine; Efficacy-Safely; Metabolism; Pharmacokinetics; Treatment and Trials

Introduction

Mechanisms of Action of Clevidipine

Clevidipine, a dihydropyridine, is a multiple Ca^{2+} channel blocker approved for clinical use. An increased concentration of cytosolic Ca^{2+} causes increased concentration in both cardiac and vascular smooth muscle cells. In cardiac myocytes, the entry of extracellular Ca^{2+} causes a larger Ca^{2+} release from intracellular stores (Ca^{2+}-induced Ca^{2+}release) and thereby initiates the contraction twitch. In smooth muscle cells, entry of Ca^{2+} plays a dominant role, but the release of Ca^{2+} from the intracellular storage sites also contributes to contraction of vascular smooth muscle, particularly in some vascular beds. Cytosolic Ca^{2+} concentrations can be increased by diverse contractile stimuli in vascular smooth cells. Many hormones and autacoids increase Ca^{2+} influx through so-called receptor-operated channels, whereas increases in external concentration of K^{+} and depolarizing electrical stimuli increase Ca^{2+} influx through voltage-gated or "potential operated" channels. Clevidipine produces its effects by binding to the α1 subunit of the L-type voltage-gated Ca^{2+} channels and lowering Ca^{2+} flux through the channel [1].

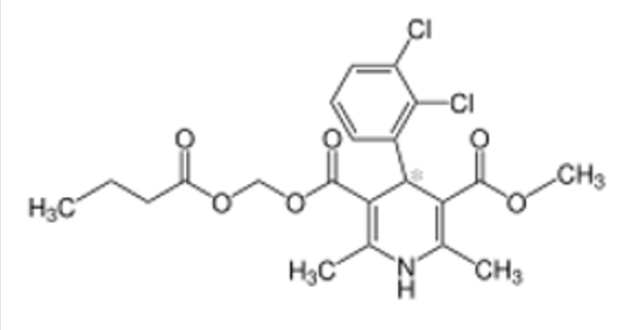
Pharmacological Actions of Clevidipine

Clevidipine is a third generation dihydropyridine calcium blocker for intravenous management of moderate to severe hypertension. Clevidipine is an ultra-short-acting selective arteriolar vasodilator that acts similar to other L-type dihydropyridine calcium channel blocker by inhibiting the influx of extracellular calcium into the vascular smooth muscle. Depolarization of vascular smooth muscle cells depends primarily on the influx of Ca^{2+}. At least three distinct mechanisms may be responsible for contraction of vascular smooth cells. First, voltage-gated Ca^{2+} channels open in response to depolarisation of the membrane, and extracellular Ca^{2+} moves down its electrochemical gradient into the cell. After closure of Ca^{2+} channels, a finite period of time is required before the channels open again in response

to a stimulus. Second, agonist-induced contractions that occur without depolarization of the membrane result from stimulation of the Gq-phospholipase C (inositol 1,4,5-triphosphate) pathway, resulting in the release of intracellular Ca^{2+} from the sarcoplasmic reticulum. Emptying of intracellular Ca^{2+} stores may trigger further influx of extracellular Ca^{2+} (store-operated Ca^{2+} entry), but its relevance in smooth muscle is unresolved. Third, receptor-operated Ca^{2+} channels allow the entry of extracellular Ca^{2+} in response to receptor occupancy. An increase in cytosolic Ca^{2+} results in enhanced binding of Ca^{2+} to calmodulin. The Ca^{2+}-calmodulin complex in turn activates myosin light-chain kinase, with resulting phosphorylation of the myosin light chain. Such phosphorylation promotes interaction between actin and myosin and leads to sustained contraction of smooth muscle. Ca^{2+} channel blockers inhibit the voltage-dependent Ca^{2+} channels in vascular smooth muscle and decreases Ca^{2+} entry. Clevidipine relaxes arterial smooth muscle and thereby decrease arterial resistance, blood pressure, and cardiac afterload [1].

Absorption, Distribution, Metabolism, and Elimination of Clevidipine

Clevidipine is administered by intravenous infusion. Clevidipine was intravenously infused at a rate ranging from 2 to 16 mg/h and clevidipine peak concentration varies with the infusion rate and ranges from 3.36 to 15.8 ng/ml. Clevidipine is rapidly eliminated and the elimination of clevidipine consists in two phases. The half-life of the initial phase is approximately 3.5 minutes and that of the terminal phase is approximately 33 minutes and the elimination half-life of the initial and terminal phases does not vary with the clevidipine infusion rate. Clevidipine consists in two enantiomers and the elimination half-life of the initial phase is approximately 2 minutes for both enantiomers whereas the elimination half-life of the terminal phase is approximately 8 minutes for (-)-R-clevidipine and is 11 minutes for (+)-S-clevidipine. Clevidipine is rapidly metabolized to the corresponding inactive metabolite H152/81 and the terminal elimination half-life of the inactive metabolite is 9.5 hours [1].



Molecular structure of clevidipine (molecular weight = 456.32 grams/mole).

Literature Search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "clevidipine efficacy, safety", "clevidipine treatment", "clevidipine adverse-effects", "clevidipine trials", "clevidipine metabolism", and "clevidipine pharmacokinetics". In addition the book: Goodman@Gilman's. The Pharmacological basis of Therapeutics [1] has been consulted.

Results

Efficacy and Safely of Clevidipine

Four studies have been reported on the efficacy and safely of clevidipine. Clevidipine was intravenously infused at a rate of 10 mg/h to 22 patients undergoing neurosurgery to lower the systolic blood pressure < 130 mmHg and the reduction of blood pressure was obtained within 15 minutes. Clevidipine effectively and safely lowers the systolic blood pressure in hypertension patients undergoing intracranial surgery [2]. Thirty-five patients with intracranial haemorrhage had a mean systolic blood pressure of 186 mmHg received clevidipine by intravenously infusion at a rate of 10 mg/h and after 5.5 minutes the systolic blood pressure was lowered from 140 to 160 mmHg. Clevidipine effectively, safely, and rapidly lowers the systolic blood pressure in patients with intracranial haemorrhage [3]. Forty-seven children with a mean age of 8.7 years undergoing neurosurgery received clevidipine by intravenous infusion at a rate of 0.5 µg/kg/min. Clevidipine effectively and safely maintain intracranial pressure and cerebral perfusion pressure without causing adverse-effects in children undergoing neurosurgery [4]. A total of 1,512 patients with acute hypertension undergoing cardiac surgery were enrolled. It was compared the efficacy and safely of clevidipine to those of nitroglycerin, to those of sodium nitroprusside, and to those of nicardipine in treatment of perioperative acute hypertension in patients undergoing cardiac surgery. Clevidipine was more effective than nitroglycerin (P-value = 0.0006) or than sodium nitroprusside (P-value = 0.003) in maintaining the blood pressure within the proper range. Clevid-

ipine was equivalent to nitroglycerin in keeping patients within the proper blood pressure range. Clevidipine effectively and safely lowers blood pressure in hypertensive patients undergoing cardiac surgery [5]. Therefore, clevidipine effectively and safely lowers the systolic blood pressure in patients undergoing intracranial surgery and in patients with intracranial haemorrhage. Clevidipine effectively and safely maintain intracranial pressure and cerebral perfusion in children undergoing neurosurgery, and clevidipine is more effective than nitroglycerin and sodium nitroprusside and is effective as nitroglycerin in in maintaining the proper blood pressure in hypertensive patients undergoing cardiac surgery.

Treatment of Hypertensive Patients with Clevidipine

Six studies have been reported on the treatment of hypertensive patients with clevidipine. Deeks, Keating, and Keam [6] reviewed the pharmacologic properties, the therapeutic efficacy, and the tolerability of clevidipine in hypertensive patients. Clevidipine inhibits L-type calcium channels in a voltage-dependent manner and exhibits a high degree of vascular selectively in-vitro. Intravenous clevidipine is effective in treatment of both acute preoperative and postoperative hypertension in adult cardiac surgery patients and with a rapid onset and short duration of action the drug can be easily titrated for blood pressure control. Moreover, in terms of controlling acutely elevated blood pressure in this patient population, clevidipine is more effective than sodium nitroprusside or nitroglycerin in the perioperative setting, and has an efficacy not different to that of nicardipine on the postoperative setting. Clevidipine is generally well-tolerated in these patient populations, and has a safely profile generally similar to that of sodium nitroprusside, nitroglycerin or nicardipine in cardiac surgery population. The blood pressure lowering effects of clevidipine are rapid and dose dependent and are achieved by decreasing systematic vascular resistance without affecting venous capacitance vessels or cardiac filling pressures with onset of effect within 5 to 15 minutes. Stead-state concentrations of clevidipine in arterial and venous blood are rapidly attained within approximately 2 to 10 minutes in healthy volunteers receiving clevidipine by intravenous infusions at a rate 0.91 or 3.2 μg/kg/min. The relationship between intravenous clevidipine infusion dose and steady-state blood concentration was linear over wide dose ranges in patients with mild to moderate hypertension and in healthy volunteers.

Clevidipine is rapidly metabolized via hydrolysis by esterases in the blood and extravascular tissues to a major metabolite namely H152/81 that is inactive as an antihypertensive drug. Concentrations of clevidipine in the blood fall rapidly in a multiphasic fashion after termination of infusion. The elimination phase of the initial is rapid with a half-life of approximately 1 minute and accounts for the majority of clevidipine exposure after an intravenous bolus dose and for 85% to 90% of its elimination and the terminal elimination phase has a half-life of approximately 15 minutes. Clevidipine produces rapid reductions of ≥ 15% of systolic blood pressure from baseline in ≤ 6 minutes, and rapidly improves mean arterial blood pressure relative to placebo. Intravenous clevidipine administered by infusion is safe and generally well-tolerated in cardiac surgery patients with acute hypertension. Clevidipine is as safe as nitroglycerin, sodium nitroprusside, or nicardipine with regard to the incidence of myocardial infarction, stroke, or renal dysfunction in patients with preoperative or postoperative hypertension. The most common adverse-effects induced by clevidipine include atrial fibrillation and sinus tachycardia, although the incidence of such adverse-effects did not differ from that seen with nitroglycerin, sodium nitroprusside, or nicardipine. Most of adverse-effects associated with clevidipine were mild or moderate in severity and considered unrelated to study drug, with the most commonly reported being headache, nausea, chest discomfort, and vomiting. Data from animal studies suggest that clevidipine may protect against myocardial and renal injury caused by ischemia and/or reperfusion. One-hundred-five hypertensive patients scheduled for cardiac surgery had a systolic blood pressure ≥ 160 mmHg and received either clevidipine by intravenous infusion at a rate of 0.4 to 8.0 μg/kg/min or placebo.

Patients treated with clevidipine demonstrated a 92.5% rate of treatment success and a lower rate of treatment failure (P-value < 0.0001) than patients who received the placebo. Clevidipine achieved target systolic blood pressure at a median time of 6.0 minutes. A modest increase in heart rate from baseline occurred during clevidipine administration. Adverse-effects occurred at the same rate in patients treated with clevidipine and in patients who received the placebo. Therefore, clevidipine rapidly decreases the blood pressure and is well-tolerated in patients scheduled for cardiac surgery [7]. In patients with hypertension and intracerebral haemorrhage the reduction of blood pressure may attenuate the mortality rate. Thirty-five patients with a mean systolic blood pressure of 186 mmHg received clevidipine and a mean time from onset of symptoms was 5.5 hours and the patients achieved target systolic blood pressure within 30 minutes. Mild to moderate hypotension was reported in 3 patients and resolved with dose reduction or drug discontinuation. Therefore, clevidipine effectively, safely, and rapidly lowers the blood pressure in critically ill patients with intracranial haemorrhage. Patients showed minimal hematoma expansion with blood pressure reduction suggesting that the rapid blood pressure control with clevidipine may have a beneficial impact on hematoma [8]. Nicardipine and clevidipine have been commonly used in neurosurgical settings. It was assessed the efficacious of clevidipine after nicardipine treatment failure in neurosurgical patients. Twelve patients treated with clevidipine after nicardipine treatment failures were included in the analysis. The median number of events that required dose-titration was 20 in patients treated with nicardipine and 17 in patients treated with clevidipine (P-value = 0.534). The median percentage of time spent at targeted systolic blood pressure goal was 76.2% in patients treated with nicardipine and 93.4% in patients treated with clevidipine (P-value = 0.123).

Therefore, clevidipine could be an alternative effective drug with acceptable benefit/risk ratio in the neurosurgical population that fails to achieve blood pressure control with nicardipine treatment [9]. Evidence suggests that clevidipine may provide faster blood pressure reduction with less volume than nicardipine in patients with stroke and in patients undergoing cardiothoracic surgery. One-hundred-eight-two patients were included in the study (103 patients received nicardipine and 79 patients received clevidipine). The time to achieve the goal blood pressure was 35 minutes in patients treated with clevidipine and 33 minutes in patients treated with nicardipine (P-value = 0.37). The infusion volume was significantly less with clevidipine (222 ml versus 518 ml; P-value = 0.01); however, the total infusion volume received in the intensive care unit was similar (3,370 ml versus 3,383 ml (P-value = 0.43). The percent time achieved the goal blood pressure range was similar (43.1% with clevidipine versus 42.3% with nicardipine). Therefore, the time to achieve goal blood pressure is similar for clevidipine and nicardipine and any decreases in medication-associated volume with clevidipine are no longer evident when all volume sources are considered. Thus clevidipine may not provide meaningful benefit in this heterogeneous population [10]. Twenty-five healthy volunteers received clevidipine by intravenous infusion at a rate of 0.12 to 48 nmol/min/kg for 20 minutes. There was a linear relationship between blood concentration and dose rate. The mean clearance was 0.121 L/min/kg and the distribution volume at steady-state was 0.56 L/kg. The half-life of the initial phase was 1.8 minutes and contributed to > 80% to the total area under the blood concentration-time curve following intravenous bolus administration and the terminal half-life was 9.5 minutes.

At the highest dose rates, the median arterial pressure was reduced by approximately 10%, and the over heart rate was > 120 beats/min. Therefore, clevidipine is a high clearance drug with extremely short half-life, is well-tolerated and is safe in healthy volunteers receiving an infusion rate up to at least 48 nmol/min/kg. The effect of clevidipine on the blood pressure was marginal, probably due to compensatory baroreflex activation in healthy volunteers [11].

Adverse-Effects Induced by Clevidipine in Hypertensive Patients

Three studies have been reported on the adverse-effects induced by clevidipine in hypertensive patients. Nguyen, Ma, and Pham [12] assessed the rate of adverse-effects induced by clevidipine and those induced by placebo in hypertensive patients. Patients received either clevidipine or placebo and the mean reduction of arterial pressure from baseline occurred in 31.2% of patients who received clevidipine and in 11.2% of patients who received placebo (P-value < 0.001). The adverse-effects included: atrial fibrillation which occurred in 13.0% to 36.1% of patients who received clevidipine and it occurred in 12.0% of patients who received placebo, nausea occurred in 5.0% to 12.0% of patients who received clevidipine and it occurred in 12.0% of patients who received the placebo, fever occurred in 19.0% of patients who received clevidipine and it occurred in 13.7% of patients who received placebo, insomnia occurred in 12% of patients who received clevidipine and occurred in 6.1% of patients who received placebo, and the acute renal failure occurred in 9.0% of patients who received clevidipine and occurred in 2.0% of patients who received the placebo. Therefore, clevidipine and placebo induce similar rate of adverse-effects thus clevidipine causes minimal adverse-effects in hypertensive patients and is well-tolerated. Clevidipine was administered to hypertensive patients and caused the following adverse-effects: atrial fibrillation, nausea, headache, and acute renal failure [13]. Clevidipine was administered to hypertensive patients and the most frequent adverse-effects reported were: atrial fibrillation, headache, nausea, vomiting, and acute renal failure [14]. Therefore, clevidipine induces some adverse-effects in hypertensive patients but they occur in a limited rate thus clevidipine is well-tolerated.

Trials Conducted with Clevidipine in Hypertensive Patients

Three studies have been reported on trials conducted with clevidipine in hypertensive patients. A prospective, randomized, open-label, and parallel-comparative trial compared the safely and the efficacy of clevidipine alone, versus those of clevidipine plus nitroglycerin, versus those of clevidipine plus sodium nitroprusside, and versus those of clevidipine plus nicardipine in hypertensive patients undergoing cardiac surgery. No difference in the incidence of myocardial infarction, stroke, or renal dysfunction was observed in these treatment groups. The mortality rate was similar in patients treated with clevidipine plus nitroglycerin and in patients treated with clevidipine plus nicardipine, whereas the mortality rate appeared to be greater in patients treated with clevidipine plus sodium nitroprusside than in patients treated with clevidipine (P-value = 0.04). The control of blood pressure was significantly more efficacious in patients treated with clevidipine than in patients treated with clevidipine plus nitroglycerin (P-value = 0.0006) and in patients treated with clevidipine plus sodium nitroprusside (P-value = 0.003) and fewer blood pressure excursions were similar in patients treated with clevidipine plus nicardipine and in patients treated with clevidipine. Therefore, clevidipine and the other treatment groups are similarly safe with the exception for the mortality rate which is greater in patients treated with sodium nitroprusside than in patients treated with clevidipine. Clevidipine controls the blood pressure more effectively than clevidipine plus nitroglycerin and clevidipine plus sodium nitroprusside [15]. A randomized, double-blind trial was conducted in 100 patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. Clevidipine was intravenously infused at a rate of 0.2 to 8 μg/kg/min or nitroglycerin was intravenously infused at a rate of 0.4 μg/kg/min from induction of anaesthesia through 12 hours postoperatively. The total mean dose pre-bypass was 4.5±4.7 mg for clevidipine and was 6.9±5.4 mg for nitroglycerin (P-value < 0.05).

The geometric mean of the area under the concentration-time curve was 283 mmHg*min/h for clevidipine (N = 45) and was 292 mmHg*min/h or nitroglycerin (N = 48). The geometric mean of the area under the concentration-time curve during aortic cannulation was 357.7 mmHg*min/h for clevidipine and was 190.5 mmHg*min/h for nitroglycerin (P-value < 0.05). The heart rate following clevidipine administration was 76.0±13.8 beats/min and it was 81.5±14.4 beats/min following nitroglycerin administration. There were no clinically important differences in adverse-effects for clevidipine and nitroglycerin. Therefore, during coronary artery bypass grafting, clevidipine is not inferior to nitroglycerin for blood pressure control and clevidipine and nitroglycerin have been found to be well-tolerated [16]. A prospective, randomized, and open-label trial compared the safety and the antihypertensive effect of clevidipine to those of nitroglycerin and to those of sodium nitroprusside preoperatively and to those of nicardipine postoperatively in patients undergoing cardiac surgery. A total of 1,512 patients were randomized 1:1 for each three parallel comparator treatment groups. The primary outcome was the incidence of death, myocardial infarction, stroke, or renal dysfunction at 30 days postoperatively. Adequacy and precision blood pressure control was evaluated and reported as a secondary outcome. There was no difference in the incidence of myocardial infarction, stroke, or renal dysfunction for patients treated with clevidipine or with other drugs. There was no difference in mortality rate between patients treated with clevidipine, with nitroglycerin, or with nicardipine. The mortality rate was significantly higher in patients treated with sodium nitroprusside than in patients treated with clevidipine (P-value = 0.04).

Clevidipine was more effective than nitroglycerin (P-value = 0.0006) or sodium nitroprusside (P-value = 0.003) in maintaining the blood pressure within the pre-specified blood pressure range. Clevidipine was equivalent to nicardipine in keeping patients within a pre-specified blood pressure range; however, when the blood pressure range was narrowed, clevidipine was associated with fewer blood pressure excursions beyond these blood pressure limits compared to nicardipine. Therefore, clevidipine is a safe and is an effective treatment of acute hypertension in patients undergoing cardiac surgery [17].

Metabolism of Clevidipine

Two studies have been reported on the metabolism of clevidipine. Clevidipine is rapidly metabolized by esterases in blood and in tissues therefore its metabolism is not affected by renal or hepatic function. Eight healthy male volunteers received 1,030 nmol/min of clevidipine together with a tracer dose of 3[H]-clevidipine for 1 hour by intravenous infusion. Frequent venous blood samples and effect recordings were obtained during ongoing infusion and up to 32 hours following termination of the infusion. The elimination half-life of the initial phase was 1.6±0.3 minutes, and the elimination half-life of the terminal phase was 15±5 minutes. The maximum concentration of the metabolite H152/81 was reached 2.2±1.3 minutes following termination of the infusion. The mean terminal half-life of inactive metabolite was 9.5±0.8 hours and the mean recovery of the radioactive in the urine reached 83±3% of the administered dose of clevidipine. Clevidipine is a high clearance drug which is rapidly metabolized to the corresponding inactive acid metabolite H152/81. The time to reach the peak concentration of the metabolite is virtually identical to the half-life of the initial elimination half-life of clevidipine. The duration of antihypertensive effect of clevidipine is short [18]. Clevidipine is likely to be co-medicated and the potential for clevidipine and its metabolite H152/81 to elicit drug interactions by induction or inhibition of cytochrome P450 was investigated. Induction of CYP1A2, CYP2C9, and CYP3A4 was examined in primary human hepatocytes treated with clevidipine at the concentrations of 1, 10, and 100 μM.

Clevidipine was found to be an inducer of CYP3A4, but not of CYP1A2 in the sale line or CYP2C9, at the concentrations of 10 μM and 100 μM. Using cDNA-expressed enzymes, clevidipine inhibited CYP2C9, CYP2C19, and CYP3A4 activities with IC_{50} values below 10 μM, whereas CYP1A2, CYP2D6, and CYP2E1 activities were not substantially inhibited and the IC_{50} values were > 70 μM and little or no inhibition of H152/81 was found for the enzyme activities with IC_{50} values ≥ 69 μM. Therefore, it is highly unlikely for clevidipine or its metabolite H152/81 to cause cytochrome P450-related drug interactions when used in the dose range required to manage hypertension in humans [19].

Pharmacokinetics of Clevidipine

Clevidipine is a rapidly-acting intravenous dihydropyridine antihypertensive acting via calcium channel blockade. Smith, et al. [20] studied the pharmacokinetics of clevidipine following the intravenous infusion of clevidipine at the infusion rate of 2, 4, 8, and 16 mg/h in 61 patients with mild to moderate hypertension. Intravenous infusion of clevidipine was initiated at a rate of 2 mg/h and force-titrated in doubling increments every 3 minutes to the target dose then maintained for 72 hours. Clevidipine blood concentrations were obtained during infusion and for 1 hour after infusion termination. The study was conducted using a randomized, single-blind, placebo-controlled, parallel-group design. Men and women aged 18 to 80 years with a history of mild to moderate hypertension were screened. To be eligible for study inclusion, patients had to be assessed in the untreated state with systolic blood pressure ≥ 140 mmHg and < 200 mmHg and/or a diastolic blood pressure ≥ 95 mmHg and < 115 mmHg, and the heart rate < 120 beats per minute. Exclusion criteria included treatment with ≥ 5 oral antihypertensive agents, secondary hypertension, myocardial infarction, or cerebrovascular events within 6 months, congestive heart failure or other severe cardiovascular disease, prior cerebral haemorrhage or intracranial tumour, liver failure or cirrhosis, intolerance to calcium channel blockers, and allergy to soybean or egg lecithin. Table 1 summarizes the pharmacokinetic parameters of clevidipine which were obtained following the intravenous infusion of clevidipine at the rate of 2, 4, 8, and 16 mg/h to 61 patients with mild to moderate hypertension. NC = not calculated. AUC0-t = area

under the concentration-time curve from zero to the last quantifiable concentration. aN = 8, bN = 6, cN = 9. This table shows that the peak concentration, the area under the concentration-time curve, and the concentration at the steady-state increase with the clevidipine dose whereas the and the total body clearance and the elimination half-life of initial and terminal phases do not vary with the clevidipine dose.

Table 1: Pharmacokinetic parameters of clevidipine which have been obtained in 61 patients with mild to moderate hypertension. The infusion rate of clevidipine was 2, 4, 8, and 16 mg/h. Values are the mean+SD, by Smith, et al. [20].

Clevidipine infusion rate	Number of determinations	Peak conc. (ng/ml)	AUC_{0-t} (ng*h/ml)	Concentration at steady-state (ng/ml)	Total body clearance (L/min)	Elimination half-life of initial phase (minutes)	Elimination half-life of terminal phase (minutes)
2	10	3.36±1.35	122±56	1.37±0.70	33.2±21.0	4.18±2.59[a]	NC
4	10	5.17±1.67	211±92	3.00±1.25	26.1±10.9	3.28±1.06[a]	37.0±29.9[b]
8	10	7.68±2.37	327±109	5.12±1.62	28.5±9.91	3.16±1.40	32.4±33.6[a]
16	10	15.8±4.01	724±246	9.20±3.37	33.4±14.7	3.34±0.96	37.3±21.7[c]

The elimination of clevidipine consists in two phases and the elimination half-life of the initial phase is much shorter than that of terminal elimination half-life. Clevidipine is rapidly eliminated thus the pharmacokinetics of clevidipine are not saturated and the initial elimination half-life phase and terminal elimination half-life phase of clevidipine do not vary with the clevidipine dose. Ericsson, et al. [21] studied the pharmacokinetics of (-)-R-clevidipine and (+)-S-clevidipine enantiomers following the intravenous infusion of clevidipine racemate to hypertensive patients. Twenty patients received three out of five randomized treatments with clevidipine. The pharmacokinetics of separate enantiomers were evaluated by compartmental analysis of blood concentrations versus time curves using population approach. The derived pharmacokinetic parameters were used to simulate the time for 50% and 90% post-infusion decline following various infusion times of clevidipine racemate. A two-compartment model was used to describe the dispositions of the enantiomers; there were only minor differences between the estimated pharmacokinetic parameters of the separate enantiomers. The mean blood clearance values of (-)-R-clevidipine and (+)-S-clevidipine were 0.103 and 0.096 L/min/kg, respectively, and the corresponding distribution volume at steady-state was 0.39 and 0.54 L/kg, respectively. The elimination of clevidipine consists in two phases and the elimination half-life of the first phase was approximately 2 minutes regardless of stereochemical configuration, and the elimination half-life of the terminal phase was approximately 8 minutes for (-)-R-clevidipine and 11 minutes for (+)-S-clevidipine and a 90% decline in concentration was achieved approximately 8 minutes post-infusion. Therefore, both enantiomers are high-clearance compounds with similar blood clearance values. The distribution volume for the enantiomers is slightly different, presumably due to differences in the protein binding. From a pharmacokinetic point of view, the use of a single enantiomer as an alternative to the racemic clevidipine will not offer any clinical advantages.

Discussion

Clevidipine, a third generation dihydropyridine, is a multiple Ca^{2+} channel blocker approved for clinical use. Clevidipine is a calcium blocker and is used for intravenous management of moderate to severe hypertension. Clevidipine is an ultra-short-acting selective arteriolar vasodilator that acts similarly to other L-type dihydropyridine calcium channel blocker by inhibiting the influx of extracellular calcium into the vascular smooth muscle [1]. The efficacy and safely of clevidipine have been reviewed. Clevidipine, intravenously infused at a rate of 10 mg/h, effectively and safely lowers the systolic blood pressure to < 130 mmHg in patients undergoing neurosurgery [2], clevidipine, intravenously infused at a rate of 10 mg/h, effectively and safely lowers the systolic blood pressure from 140 to 160 mmHg in patients with intracranial haemorrhage [3], clevidipine, intravenously infused at a rate of 0.5 μg/kg/min effectively and safely maintain intracranial pressure and cerebral perfusion in children undergoing neurosurgery [4], and clevidipine is more effective than nitroglycerin (P-value = 0.0006) and sodium nitroprusside (P-value = 0.003) and is equivalent to nitroglycerin in maintaining blood pressure within the proper range in patients with acute hypertension undergoing cardiac surgery [5]. The treatment of hypertensive patients with clevidipine has been reviewed. Deeks, Keating, and Kean [6] reviewed the pharmacologic properties, the therapy efficacy, and the tolerability of clevidipine in hypertensive patients.

Clevidipine inhibits L-type calcium channels in a voltage-dependent manner and inhibits a high degree of vascular selectively in-vitro. Clevidipine effectively treats both acute preoperative and postoperative hypertension in patients undergoing cardiac surgery, and clevidipine is more effective than sodium nitroprusside and nitroglycerin and is effective as nicardipine in controlling blood pressure in patients on the postoperative setting. Clevidipine lowers blood pressure rapidly and the decrease of vascular resistance in dose dependent and lowers the vascular resistance approximately within 5 to 15 minutes. Clevidipine infused at the rate of 0.91 or 3.2 μg/kg/min lowers blood pressure within 2 or 10 minutes. Clevidipine is rapidly metabolized via hydrolysis by esterases in blood and extravascular tissues to an inactive metabolite namely H152/81. The elimination of clevidipine in the blood is rapid and consists in two phases. The elimination half-life of the initial phase is approximately 1 minute and ac-

counts for 85% to 90% of clevidipine elimination. The half-life of the terminal phase is approximately 15 minutes and clevidipine reduces ≥ 15% from baseline in systolic blood pressure in ≤ 6 minutes. Clevidipine intravenously infused is found to be safe and well-tolerated in patients with acute hypertension undergoing cardiac surgery. Clevidipine is safe as nitroglycerin, sodium nitroprusside, or nicardipine with regard to the incidence of myocardial infarction, stroke, or renal dysfunction in patients with postoperative hypertension. The most common adverse-effects induced by clevidipine include atrial fibrillation and sinus tachycardia and these adverse-effects are similar to those induced by nitroglycerin, sodium nitroprusside, or nicardipine and the adverse-effects induced by clevidipine are mild or moderate in severity.

Other adverse-effects are headache, nausea, chest discomfort, and vomiting. Patients undergoing cardiac surgery had a systolic blood pressure ≥ 160 mmHg and received either clevidipine infused at a rate of 0.4 to 8.0 μg/kg/min or placebo. Patients treated with clevidipine have a success rate of 92.5% and a lower rate of treatment failure (P-value < 0.0001) than patients who received the placebo. Clevidipine achieved target systolic blood pressure at a median time of 6.0 minutes. A modest increase in heart rate occurs during clevidipine administration and the adverse-effects occur at the same rate in patients treated with clevidipine and in patients who receive placebo [7], in patients with hypertension and intracerebral haemorrhage the reduction of blood pressure may attenuate the mortality rate. Patients with a mean systolic blood pressure of 186 mmHg received clevidipine and the mean time from onset of symptoms is 5.5 hours. Patients achieved target systolic blood pressure within 30 minutes and mild to moderate hypotension was reported in 8.6% of patients [8], it was assessed the effectivity of clevidipine after nicardipine treatment failure in neurosurgical setting. The median number of events required for dose-titration is 20.5 in patients treated with nicardipine and 17 in patients treated with clevidipine (P-value = 0.534). The median percentage of time spent to target systolic blood pressure goal is 76.2 and 93.4 in patients treated with nicardipine and clevidipine, respectively (P-value = 0.123). Therefore, clevidipine is an alternative effecting drug with similar benefit/risk ratio in the neurosurgical population that fails to achieve blood pressure control with nicardipine treatment [9], clevidipine provides faster reduction in blood pressure than nicardipine.

The time to achieve goal blood pressure is 35 and 33 minutes in patients treated with clevidipine and nicardipine, respectively (P-value = 0.37) and the time to guideline-directed 25% reduction was similar (P-value = 0.42) in patients treated with clevidipine or with nicardipine. The volume from study drug is less with clevidipine than with nicardipine (P-value < 0.01) however the total volume received in the intensive care unit is similar with clevidipine and nicardipine (P-value = 0.43). Therefore, the time to achieve goal blood pressure is similar for clevidipine and nicardipine thus clevidipine may provide meaningful benefit in this population [10], healthy volunteers received clevidipine by intravenous infusion at a rate of 0.12 to 48 nmol/min/kg for 20 minutes and there was a linear relationship between blood concentration and dose rate. The mean clearance is 0.121 L/min/kg and the distribution volume at steady-state is 0.56 L/kg. The initial half-life is 1.8 minutes and contributes to > 80% to the total area under the blood concentration-time curve following intravenous bolus administration and the terminal half-life is 9.5 minutes. At the highest dose rate, the median arterial pressure is reduced by approximately 10% and the over heart rate is > 120 beats/min. Therefore, clevidipine is a high clearance drug with extremely short half-life, is well-tolerated and is safe in healthy volunteers and the effect of clevidipine on blood pressure is marginal probably due to compensatory baroreflex activation in healthy volunteers [11]. The adverse-effects induced by clevidipine in hypertensive patients have been reviewed. Nguyen, Ma, and Pham [12] assessed the rate of adverse-effects induced by clevidipine and those induced by placebo in hypertensive patients. The mean reduction of arterial from baseline occurs in 31.2% of patients treated with clevidipine and in 11.2% of patients who received placebo (P-value < 0.001).

The adverse-effects included: atrial fibrillation which occurs in 13.0% to 36.1% of patients who received clevidipine and it occurred in 12.0% in patients who received placebo, nausea, fever, insomnia and acute renal failure occur in similar rate in patients treated with clevidipine and in patients who received placebo. Therefore, clevidipine induces adverse-effects at a similar rate of those induced by placebo. Clevidipine induces the following adverse-effects: atrial fibrillation, nausea, headache, and renal failure [13], and the adverse-effects induced by clevidipine are: atrial fibrillation, headache, nausea, vomiting, and acute renal failure. Therefore, clevidipine induces some adverse-effects in hypertensive patients but they occur in a limited rate thus clevidipine is a safe drug [14]. The trials conducted with clevidipine in hypertensive patients have been reviewed. A prospective, randomized, open-label, and parallel-comparative trial compared the safety and the efficacy of clevidipine alone, versus those of clevidipine plus nitroglycerin, versus those of clevidipine plus sodium nitroprusside, and versus those of clevidipine plus nicardipine in hypertensive patients undergoing cardiac surgery. No differences in the incidence of myocardial infarction, stroke, or renal dysfunction were observed in the treatment groups. The mortality rate was similar in patients treated with clevidipine plus nitroglycerin and in patients treated with clevidipine plus nicardipine, whereas the mortality rate was greater in patients treated with clevidipine plus sodium nitroprusside than in patients treated with clevidipine (P-value = 0.04). The control of blood pressure was significantly more effective in patients treated with clevidipine than in patients treated with clevidipine plus nitroglycerin (P-value = 0.0006) and in patients treated with clevidipine plus sodium nitroprusside (P-value = 0.003) and fewer blood pressure excursions were similar in patients treated with clevidipine plus nicardipine and in patients treated with clevidipine.

Therefore, clevidipine and the other treatment groups are similar safe with the exception for the mortality rate which is greater in patients treated with sodium nitroprusside than in patients treated with clevidipine. Clevidipine controls the blood pressure more effectively than clevidipine plus nitroglycerin and clevidipine plus nitroprusside [15], a randomized, double-blind trial was conducted in 100 patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. Clevidipine was intravenously infused at a rate of 0.2 to 8 μg/kg/min or nitroglycerin was intravenously infused at a rate of 0.4 μg/kg/min from induction of anaesthesia through 12 hours postoperatively. Total mean dose pre-bypass was 4.5±4.7 mg for clevidipine and was 6.9±5.4 mg for nitroglycerin (P-value < 0.05). The geometric mean of the area under the concentration-time curve was 283 mmHg*min/h for clevidipine (N = 45) and was 292 mmHg*min/h for nitroglycerin (N = 48). The geometric mean of the rea under the concentration-time curve during aortic cannulation was 357.7 mmHg*min/h for clevidipine and was 190.5 mmHg*min/h for nitroglycerin (P-value < 0.05). The heart rate following clevidipine administration was 76.0±13.8 beats/min and it was 81.5±14.4 beats/min following nitroglycerin administration. There were no clinically important differences in adverse-effects for clevidipine and nitroglycerin. Therefore, during artery bypass grafting, clevidipine is not inferior to nitroglycerin for blood pressure control and clevidipine and nitroglycerin have been found to be well-tolerated [16], a prospective, randomized, and open-label trial compared the safety and the antihypertensive effect of clevidipine to those of nitroglycerin and to those of sodium nitroprusside preoperatively and to those of nicardipine postoperatively in patients undergoing cardiac surgery.

A total of 1,512 patients were randomized 1:1 for each the three parallel comparator treatment groups. The primary outcome was the incidence of death, myocardial infarction, stroke, or renal dysfunction at 30 days postoperatively. Adequacy and precision blood control were evaluated and reported as a secondary outcome. There were no differences in the incidence of myocardial infarction, stroke, or renal dysfunction for patients treated with clevidipine, with nitroglycerin, or with nitroglycerin. The mortality rate was significantly higher in patients treated with sodium nitroprusside than in patients treated with clevidipine (P-value = 0.0006) or sodium nitroprusside (P-value = 0.003) in maintain the blood pressure within the pre-specified blood pressure range. Clevidipine was equivalent to nicardipine in keeping patients within a pre-specified blood pressure range; however, when the blood pressure range was narrowed, clevidipine was associated with fewer blood pressure excursions beyond these blood pressure limits compared to nicardipine. Therefore, clevidipine is a safe and effective treatment for acute hypertension in patients undergoing cardiac surgery [17]. The metabolism of clevidipine has been reviewed. Clevidipine is rapidly metabolized by esterases in blood and in tissues therefore its metabolism is not affected by renal or hepatic function. Eight healthy male volunteers received 1,030 nmol/min of clevidipine together with a tracer dose of 3[H]-clevidipine for 1 hour by intravenous infusion. The elimination half-life of the initial phase was 1.6±0.3 minutes and the elimination half-life of the terminal phase was 15±5 minutes. The maximum concentration of the metabolite H152/81 was reached 2.2±1.3 minutes following termination of the infusion.

The mean terminal half-life of the inactive metabolite was 9.5±0.8 hours and the mean recovery of the radioactive in the urine reached 83±3% of the administered dose of clevidipine. Clevidipine is a high clearance drug which is rapidly metabolized to the corresponding inactive metabolite H152/81. The time to reach the peak concentration of the metabolite is virtually identical to the half-life of the initial elimination half-life of clevidipine [18], clevidipine is likely to be co-medicated and the potential for clevidipine and its metabolite H152/81 to elicit drug interactions by induction or inhibition of cytochrome P450 was investigated. Induction of CYP1A2, CYP2C9, and CYP3A4 was examined in primary human hepatocytes treated with clevidipine at the concentrations of 1, 10, and 100 μM. Clevidipine was found to be an inducer of CYP3A4, but not of CYP1A2 or CYP2C9, at the concentration of 10 μM and 100 μM. Using cDNA-expressed enzymes, clevidipine inhibited CYP2C9, CYP2C19, and CYP3A4 activities with IC_{50} values below 10 μM, whereas CYP1A2, CYP2D6, and CYP2E1 activities were not substantially inhibited and the IC_{50} values were > 70 μM and little or no inhibition by H152/81 was found for the enzyme activities with IC_{50} values ≥ 69 μM. It is highly unlikely for clevidipine or its metabolite H152/81 to cause cytochrome P450-related drug interactions when used in the dose range required to manage hypertension in humans [19]. The pharmacokinetics of clevidipine has been reviewed. Smith, et al. [20] studied the pharmacokinetics of clevidipine following the intravenous infusion of clevidipine at the rate of 2, 4, 8, and 16 mg/h in 61 patients with mild to moderate hypertension.

The peak concentration of clevidipine ranged from 3.36±1.35 to 15.8±4.01 ng/ml and increased with clevidipine dose, the area under the concentration-time curve of clevidipine ranged from 122±56 to 724±246 ng*h/ml and increased with clevidipine dose, the clevidipine concentration at the stead-state ranged from 1.37±0.70 to 9.20±3.37 ng/ml and increased with clevidipine dose, whereas the total body clearance, the elimination half-life of the initial phase, and the elimination half-life of the terminal phase remained constant according to the clevidipine dose and were about 33 L/min, 3 minutes, and 37 minutes, respectively. Ericsson, et al. [21] studied the pharmacokinetics of (-)-R-clevidipine and (+)-S-clevidipine following intravenous infusion of clevidipine racemate to hypertensive patients. A two-compartment model was used to describe the disposition of the enantiomers; there were only minor differences between the estimated pharmacokinetic parameters of the separate enantiomers. The mean total blood clearance values of (-)-R-clevidipine and (+)-S-clevidipine were 0.103 and 0.096 L/min/kg, respectively, and the distribution volume at the steady-state was 0.39 and 0.54 L/kg for (-)-R-clevidipine and for (+)-S-clevidipine, respectively. The elimination of clevidipine con-

sists in two phases and the elimination half-life of the first phase was approximately 2 minutes regardless of stereochemical configuration, and the elimination half-life of the terminal phase was approximately 8 minutes for (+)-R-clevidipine and 11 minutes for (+)-S-clevidipine and a 90% decline in concentration was achieved approximately 8 minutes post-infusion. Therefore, both enantiomers are high-clearance compounds with similar blood clearance values. The distribution volume for the enantiomers is slightly different, presumably due to differences in the protein binding. From a pharmacokinetic point of view, the use of a single enantiomer as an alternative to the racemic clevidipine will not offer any clinical advantages.

In conclusion, clevidipine is administered by intravenous infusion. Clevidipine is a third generation dihydropyridine calcium blocker for intravenous management of moderate to severe hypertension. Clevidipine is an ultra-short-acting selective arteriolar vasodilator that acts similar to other L-type dihydropyridine calcium channel blockers by inhibiting the influx of extracellular calcium into the vascular smooth muscle. The efficacy and safely of clevidipine, the treatment of hypertensive patients with clevidipine, and the trials conducted with clevidipine in hypertensive patients have been reviewed. Clevidipine induces adverse-effects in hypertensive patients such as: atrial fibrillation, headache, vomiting, and acute renal failure and a study revealed that the adverse-effects induced by clevidipine occur at a similar rate in patients who received placebo. Clevidipine is metabolized into the inactive metabolite namely H152/81 and clevidipine induces or inhibits some cytochromes P450. The pharmacokinetics of clevidipine have been reviewed. Clevidipine is administered at the infusion rate of 2, 4, 8, and 16 mg/h and clevidipine elimination consist in two phases. The initial elimination half-life of clevidipine is shorter than the terminal elimination half-life of clevidipine. Clevidipine peak concentration, the area under the concentration-time curve of clevidipine, and the clevidipine concentration at the steady-state increase with clevidipine dose whereas clevidipine total body clearance, the elimination half-life the initial and terminal phases do not vary with clevidipine concentration. Clevidipine consists of two enantiomers: (-)-R-clevidipine and (+)-S-clevidipine and the elimination half-life of the initial phase is approximately 2 minutes for both enantiomers whereas the elimination half-life of the terminal phase is approximately 8 minutes for (-)-R-clevidipine and 11 minutes for (+)-S-clevidipine. The aim of this study is to review the clinical pharmacology of clevidipine.

Conflict of Interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

Acknowledgments

The author thanks Dr. Patrizia Ciucci and Dr. Francesco Varricchio, of the Medical Library of the University of Pisa, for retrieving the scientific literature.

References

1. Escenhagen T (2023) Treatment of Ischemic Heart Disease. In Goodman@ Gilman's. The Pharmacological Basis of Therapeutics. In: Brunton LL, Knollmann BC (Eds.,). Mc Graw Hill 14th Edition, pp. 604-624.
2. Bekker A, Didehvar S, Kim S, Golfinos JG, Parker E, et al. (2010) Efficacy of clevidipine in controlling perioperative hypertension in neurosurgical patients: initial single-center experience. J Neurosurg Anesthesiol 22(4): 330-335.
3. Graffagnino C, Bergese S, Love J, Schneider D, Lazaridis C, et al. (2013) Clevidipine rapidly and safely reduces blood pressure in acute intracerebral hemorrhage: the ACCELERATE trial. Cerebrovasc Dis 36(3): 173-180.
4. Vadasz E, Moss J, Chang N, Casazza M, Rasmussen L, et al. (2022) Effect of clevidipine on intracranial pressure in pediatric neurosurgical patients: a single-center retrospective review. J Neurosurg Pediatr 31(3): 252-257.
5. Aronson S, Dyke CM, Stierer KA, Levy JH, Cheung AT, et al. (2008) The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. Anesth Analg 107(4): 1110-1121.
6. Deeks ED, Keating GM, Keam SJ (2009) Clevidipine: a review of its use in the management of acute hypertension. Am J Cardiovasc Drugs 9(2): 117-134.
7. Levy JH, Mancao MY, Gitter R, Kereiakes DJ, Grigore A, et al. (2007) Clevidipine effectively and rapidly controls blood pressure preoperatively in cardiac surgery patients: the results of the randomized, placebo-controlled efficacy study of clevidipine assessing its preoperative antihypertensive effect in cardiac surgery. Anesth Analg 105(4): 918-925.
8. Graffagnino C, Bergese S, Love J, Schneider D, Lazaridis C, et al. (2013) Clevidipine rapidly and safely reduces blood pressure in acute intracerebral hemorrhage: the ACCELERATE trial. Cerebrovasc Dis 36(3): 173-180.
9. Borrell Vega J, Uribe AA, Palettas M, Bergese SD (2020) Clevidipine use after first-line treatment failure for perioperative hypertension in neurosurgical patients: A single-center experience. Medicine (Baltimore) 99(1): e18541.
10. Johnson L, Erdman M, Ferreira J (2024) Comparison of clevidipine vs nicardipine in the treatment of hypertensive urgency and emergency in critically ill patients. Am J Health Syst Pharm 81(21): e668-e676.
11. Ericsson H, Fakt C, Jolin Mellgård A, Nordlander M, Sohtell L, et al. (1999) Clinical and pharmacokinetic results with a new ultrashort-acting calcium antagonist, clevidipine, following gradually increasing intravenous doses to healthy volunteers. Br J Clin Pharmacol 47(5): 531-538.
12. Nguyen HM, Ma K, Pham DQ (2010) Clevidipine for the treatment of severe hypertension in adults. Clin Ther 32(1): 11-23.
13. Prlesi L, Cheng Lai A (2009) Clevidipine: a novel ultra-short-acting calcium antagonist. Cardiol Rev 17(3): 147-152.
14. Ndefo UA, Erowele GI, Ebiasah R, Green W (2010) Clevidipine: a new intravenous option for the management of acute hypertension. Am J Health Syst Pharm 67(5): 351-360.
15. Aronson S (2009) Clevidipine in the treatment of perioperative hypertension: assessing safety events in the ECLIPSE trials. Expert Rev Cardiovasc Ther 7(5): 147-52.

16. Merry AF, Avery EG, Nussmeier NA, Playford HR, Warman GR, et al. (2014) Clevidipine compared with nitroglycerin for blood pressure control in coronary artery bypass grafting: a randomized double-blind study. Can J Anaesth 61(5): 398-406.

17. Aronson S, Dyke CM, Stierer KA, Levy LH, Cheung AT, et al. (2008) The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. Anesth Analg 107(4): 1110-1121.

18. Ericsson H, Fakt C, Höglund L, Jolin Mellgård Å, Nordlander M, et al. (1999) Pharmacokinetics and pharmacodynamics of clevidipine in healthy volunteers after intravenous infusion. Eur J Clin Pharmacol 55(1): 67-67.

19. Zhang JG, Dehal SS, Ho T, Johnson J, Chandler C, et al. (2006) Human cytochrome p450 induction and inhibition potential of clevidipine and its primary metabolite H152/81. Drug Metab Dispos 34(5): 734-737.

20. Smith WB, Marbury TC, Komjathy SF, Sumeray MS, Williams GC, et al. (2012) Pharmacokinetics, pharmacodynamics, and safety of clevidipine after prolonged continuous infusion in subjects with mild to moderate essential hypertension. Eur J Clin Pharmacol 68(10): 1385-1394.

21. Ericsson H, Schwieler J, Lindmark BO, Löfdahl P, Thulin T, et al. (2001) Enantioselective pharmacokinetics of the enantiomers of clevidipine following intravenous infusion of the racemate in essential hypertensive patients. Chirality 13(3): 130-134.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2025.61.009563

Gian Maria Pacifici. Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php