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Clevidipine: A Unique Agent for the Critical Care Practitioner

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Abstract

Clevidipine is a new third generation intravenous dihydropyridine calcium channel blocker. It is a specific arterial vasodilator developed for the acute reduction and control of arterial blood pressure in the perioperative period. This drug has an extremely short half life and is rapidly metabolized by tissue and plasma esterases. Clevidipine is a potent arterial vasodilator with very little or no effect of the myocardial contractility and venous capacitance and also minimal side effects. Clevidipine can also theoretically help to protect against organ reperfusion injury. Theoretically, this effect resides in the capacity of this agent to debilitate oxygen free radical-mediated toxicity, cell calcium overload and augment endothelial nitric oxide bioavailability through antioxidative actions. As a result it may diminish the severity of low flow myocardial ischemia and preserve the coronary endothelial function thereby reducing the infarct size. Due to all the characteristics of this parenteral agent it promises to be the drug of choice for the critical care practitioner for the strict control of blood pressure in different clinical scenarios.

Keywords: Clevidipine, calcium channel blocker, hypertension

Introduction

Clevidipine has been recently developed for use in clinical settings where tight control blood pressure is crucial [1]. Clevidipine (butyroxymethyl methyl 4-(2', 3'-dichlorophenyl)-2, 6-dimethyl-1, 4-dyhydropyridine-3, 5-dicarboxylate) is a third generation dihydropyridine calcium antagonist specific for arterial vasodilatation [2] (Fig.1). Clevidipine acts by selectively inhibiting the influx of extracellular calcium through the L-type channel, relaxing the smooth muscle cells that line small arteries, resulting in widening of the artery opening and reducing peripheral vascular resistance [2]. It belongs to the dihydropiridine subgroup and is an ultra-short acting medication [1-3].

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Pharmacology

Clevidipine is a racemic mixture of two enantiomers S-clevidipine and R-clevidipine [4]. It is structurally similar to other calcium channel antagonist of the dihydropiridine type [3]. This agent has an additional ester linkage in the molecule that makes it different from the other dihydropiridines. Due to this ester linkage, it is rapidly metabolized by ester hydrolysis in blood and extravascular tissues to its inactive carboxylic acid metabolite (H152/81) [3-5]. This same metabolite is formed following felodipine administration [4].

Clevidipine has a mean blood flow clearance of 0.105 L/kg/min and a volume of distribution of 0.51 L/kg. The half-life is around 2 minutes, independent of stereochemical configuration. A rapid decline in plasma concentration is found, with approximately 90% of R-clevidipine being cleared in 8 minutes and 90% of the S-clevidipine cleared in 11 minutes [4,6,7]. Clevidipine and its enantiomer, are highly bound to plasma proteins (>99.5%). The free fraction on S-clevidipine is 0.43% and 0.32% for R-clevidipine; this difference in the protein binding of enantiomers might explain the difference in the volume distribution of both enantiomers [4,8].

When given intravenously, clevidipine is cleared

rapidly with a relatively small volume of distribution resulting in an extremely short half-life [9]. The contribution of blood metabolism to the total elimination is less than 10%, indicating the high ester hydrolysis activity in extravascular tissues [2,5,9,10]. The blood clearance of clevidipine exceeds liver flow by three times, and it is similar to the cardiac output [5,7-9]. For this reason it is thought that other tissues in addition to the liver are likely to contribute to the elimination [9,11].

Clevidipine's primary, inactive metabolite is excreted 68% via the urine and 15% via feces. This suggests that there is biliary elimination, or intestinal secretion, or both [9].

Blood pressure control in the critical care patient

There are certain clinical settings (i.e., hypertensive emergency, cardiac and renal failure, angina, myocardial infarction, eclampsia and following cardiac, vascular or cerebral surgery) where the strict control of blood pressure is mandatory and an increase of the mean arterial blood pressure above 90 mmHg should be lowered urgently to prevent or limit organ damage [12-14].

As we know blood pressure is dependent on the cardiac output and the peripheral vascular resistance. In the majority of the cases hypertension is due to an increase in peripheral vascular resistance.

In the present time there are several pharmacological agents used to achieve the blood pressure control. None of these agents are ideal due to their lack of selectivity, secondary effects, duration of action, etcetera.

In several studies clevidipine had shown that the effect on blood pressure is dose or infusion rate dependent, and due to the short half life it is feasible to improve blood pressure control and avoid excessive falls in blood pressure that also can lead to fatal complication in the critically ill patients.

Clevidipine is a selective arterial vasodilator with very little or no effect of the myocardial contractility and venous capacitance, and also minimal side effects (i.e., headache, flushing, increase diuresis, nausea and vomiting) [1,10]. Clevidipine seems to be an ideal agent for the critical care practitioner for the strict control of blood pressure. As clevidipine was designed for the blood pressure control in the cardiac surgical setting, studies of the use of clevidipine in other clinical scenarios should be explored.

Clevidipine and the management of perioperative hypertension

Post operative hypertension is a common complication after cardiac surgery. It has been reported that 80% of patients undergoing cardiac surgery require treatment for blood pressure control [6,15]. Perioperative hypertension has been associated with subendocardial ischemia, due to an increase in myocardial work. Bleeding and cerebrovascular hemorrhage are other possible complications. For these reasons, perioperative hypertension is an undesirable and potentially dangerous complication, and needs to be treated immediately [1,15-17].

As mentioned before, clevidipine is a specific arterial vasodilator developed for the acute reduction and control of arterial blood pressure in the perioperative setting. Its extremely short plasma half-life makes lends itself well to tight blood pressure control [1,10]. There doesn't appear to be any decrease of myocardial contractility or any effect on the venous capacitance vessels [1,10].

Studies in healthy volunteers showed that clevidipine had a minor effect on the mean arterial pressure and an increase in the heart rate, possibly due to baroreceptor activation [5,6,9] .

In other studies where the use of clevidipine was in patients under general anesthesia, a reduction of 20% in blood pressure with minimal changes in the heart rate was shown [6,9]. Clevidipine can decrease the systemic vascular resistance by approximately 27% at the highest infusion rate [10]. The decreases in systemic vascular resistance by clevidipine are dose dependent [5,10].

Clevidipine's selective arterial vasodilation has little effect on the preload, stroke volume or cardiac output and the heart rate remains stable during it administration in patients under general anesthesia [10,18].

This effect on blood pressure and heart rate reaches steady state after 15 minutes of starting the clevidipine infusion, and go back to predose values within the same short period after termination of the infusion [5,8,9].

In recent studies where clevidipine was compared with sodium nitropusside, no statistical difference was found in the reduction of the mean arterial pressure. Also the effect on the heart rate was studied, finding a greater increase in the heart rate when sodium nitroprusside was used [19].

Although the dilatation of the coronary resistance vessels cause a decrease of 30% in coronary perfusion pressure, the global myocardial blood flow is augmented during the infusion of clevidipine [10].

Clevidipine and the protective effects in reperfusion injury

The calcium channel blockers, in addition to their classic actions, can increase blood flow during ischemia via bradykinin and nitric oxide-dependent mechanisms and protect the ischemic myocardium against reperfusion injury by assuring nitric oxide bioavailability [20-23]. This injury is the result of the accumulation and activation of neutrophils, and the oxygen free radicals originated in the re-oxygenation of the ischemic tissues causing the disruption of the integrity of the cell membrane [24]. With an excess of calcium entering the cell, altering calcium homeostasis can lead to loss of mitochondrial function and consequently cell death [25].

Clevidipine can theoretically help to protect against organ reperfusion injury. This effect resides in the capacity of this agent to debilitate oxygen free radical-mediated toxicity and cell calcium overload [26]. The dihydropyridine calcium channel blockers interfere with the intracellular calcium metabolism by decreasing the transport of calcium through the membrane and by assuring calcium binding to calmodulin [26,27].

During reperfusion, the bioavailability of the nitric oxide is reduced, so dihydropyridine calcium channel blockers can release nitric oxide from coronary vessels, control oxygen consumption by the myocardium by modulating bradykinin–mediated nitric oxide release, augment endothelial nitric oxide bioavailability through antioxidative actions and diminish the severity of low flow myocardial ischemia and preserving the coronary endothelial function [24,27-31].

In experimental data, a reduction of the infarct area of up to 60% is seen when clevidipine is administered [26]. In several studies bradykinin through the β_2 receptor has help to minimize infarct size during myocardial ischemia-reperfusion [26,29,32]. The cardioprotective action of clevidipine is related to maintain the bioavailability of the nitric oxide [26,33].

Natriuretic and diuretic properties of clevidipine

Clevidipine is not only a potent arteriolar dilator, but also has natriuretic properties [34]. As is known the blockage of L-type calcium channels in the kidney elicits

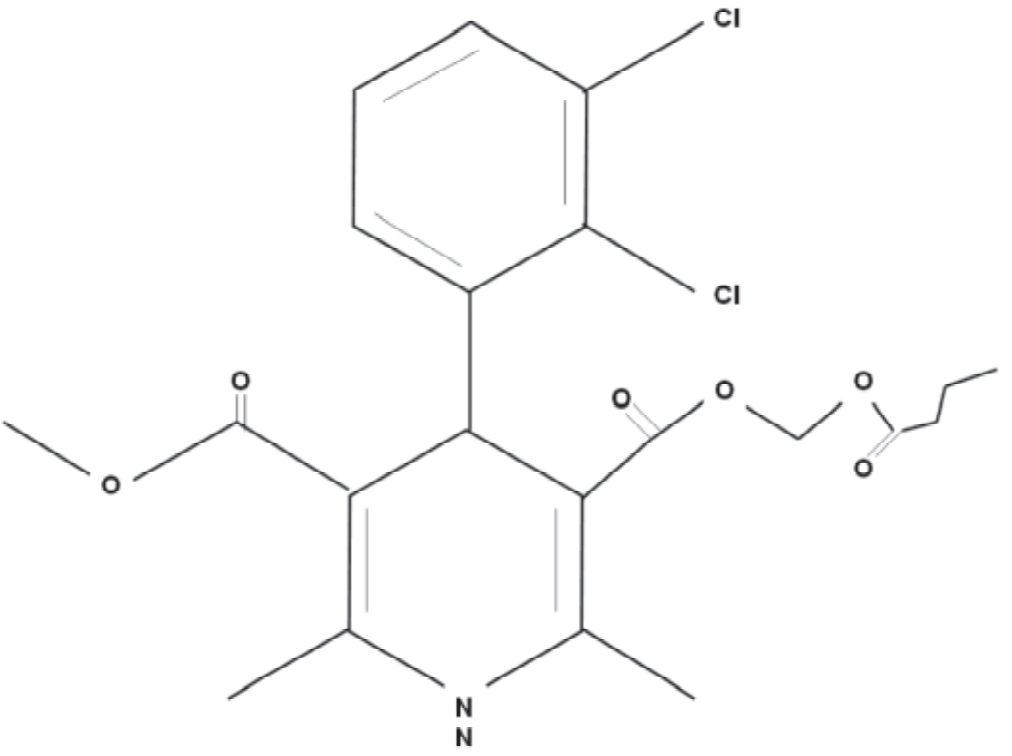

FIGURE 1. CLEVIDIPINE

marked increasing glomerular filtration rate and renal blood flow [35]. It does act on the proximal and on the distal tubes producing natriuresis and diuresis.

In a study of induced acute renal failure in rats, clevidipine attenuated the severity of the ischemic injury [34]. This is an area that is of particular importance to critical care practitioners.

Conclusions

Clevidipine promises to be the medication of choice for the reduction and control of blood pressure during and following surgery and in other critical care settings. In previous studies clevidipine has demonstrated to be a potent arterial dilator. Clevidipine has been shown to have dose and concentration-dependent decreases in mean arterial blood pressure and systemic vascular resistance, with a little effect in heart rate; no effects in venous capacitance vessels. It has also been shown to increase stroke volume with no changes in central venous pressure. A number of minor side effects are related to the mechanism of action of the medication (e.g., headache, flush, polyuria). Nausea, vomiting and dysrrhythmias were noted occasionally as well. Clevidipine seems to combine the hemodynamic effects and lack of toxicity of nicardipine with the rapid onset and offset of nitroprusside [19].

DISCLOSURE: Gabriela Rodriguez reports no conflicts of interest in the preparation of this manuscript. Joseph Varon MD, FACP, FCCP, FCCM has served as a consultant for The Medicines Company that manufacture clevidipine.

References

1. Bailey JM, Lu W, Levy JH, Ramsay JG, Shore-Lesserson L, Prielipp RC, Brister NW, Roach GW, Jolin-Mellgard A, Nordlander M (2002) Clevidipine in adult cardiac surgical patients, a dose-finding study. Anesthesiology 96:1086-1094
2. Ericsson H, Tholander B, Regardh CG (1999) In vitro hydrolysis rate and protein binding of clevidipine, a new ultrashort-acting calcium antagonist metabolised by esterases, in different animal species and man. Eur J Pharm Sci 8:29-37
3. Segawa D, Sjoquist PO, Wang QD, Gonon A, Nordlander M, Ryden L (2000) Calcium antagonist protects the myocardium from reperfusion injury by interfering with mechanisms directly related to reperfusion: an experimental study with the ultrashort-acting calcium antagonist clevidipine. J Cardiovasc Pharmacol 36:338-343
4. Ericsson H, Schwieler J, Lindmark BO, Lofdahl P, Thulin T, Regardh CG (2001) Enantioselective pharmacokinetics of the enantiomers of clevidipine following intravenous infusion of the racemate in essential hypertensive patients. Chirality 13:130-134
5. Ericsson H, Fakt C, Jolin-Mellgard A, Nordlander M, Sohtell L, Sunzel M, Regardh CG (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 47:531-538
6. Schwieler JH, Ericsson H, Lofdahl P, Thulin T, Kahan T (1999) Circulatory effects and pharmacology of clevidipine, a novel ultra short acting and vascular selective calcium antagonist, in hypertensive humans. J Cardiovasc Pharmacol 34:268-274
7. Huraux C, Makita T, Szlam F, Nordlander M, Levy JH (1997) The vasodilator effects of clevidipine on human internal mammary artery. Anesth Analg 85:1000-1004
8. Ericsson H, Bredberg U, Eriksson U, Jolin-Mellgard A, Nordlander M, Regardh CG (2000) Pharmacokinetics and arteriovenous differences in clevidipine concentration following a short and long-term intravenous infusion in healthy volunteers. Anesthesiology 92:993-1001
9. Ericsson H, Fakt C, Hoglund L, Jolin-Mellgard A, Nordlander M, Sunzel M, Regardh CG (1999) Pharmacokinetics and pharmacodynamics of clevidipine in healthy volunteers after intravenous infusion. Eur J Clin Pharmacol 55:61-67
10. Kieler-Jensen N, Jolin-Mellgard A, Nordlander M, Ricksten SE (2000) Coronary and systemic hemodynamic effects of clevidipine, an ultra-short-acting calcium antagonist, for treatment of hypertension after coronary artery surgery. Acta Anaesthesiol Scand 44:186-193
11. Vuylsteke A, Milner Q, Ericsson H, Mur D, Dunning J, Jolin-Mellgard A, Nordlander M, Latimer R (2000) Pharmacokinetics and pulmonary extraction of clevidipine, a new vasodilating ultrashort-acting dihydropyridine, during cardiopulmonary bypass. Br J Anaesth 85:683-689
12. Santhi R, Worthley L (2003) Hypertension in the critically ill patient. Crit Care Resusc 5:24-42
13. Varon J, Marik PE (2003) Clinical review: The management of hypertensive crises. Crit Care 7:374-384
14. Varon J, Marik PE (2000) The diagnosis and management of hypertensive crises. Chest 118:214-227
15. Gray RJ (1988) Postcardiac surgical hypertension. J Cardiothor Anesth 2:670-682
16. Viljoen JF, Estafanous FG, Tarazi RC (1976) Acute hypertension immediately after coronary artery surgery. J Thorac Cardiovasc Surg 71:548-550

17. Haas CE, LeBlanc JM (2004) Acute postoperative hypertension a review of therapeutic options. Am J Health Syst Pharm 61:1661-1673
18. Vuylsteke A, Feneck RO, Jolin-Mellgard A, Latimer RD, Levy JH, Lynch C 3rd, Nordlander ML, Nystrom P, Ricksten SE (2000) Perioperative blood pressure control: a perioperative survey of patient management in cardiac surgery. J Cardiothorac Vasc Anesth 14:269-273
19. Powroznyk AV, Vuylsteke A, Naughton C, Misso SL, Holloway J, Jolin-Mellgard A, Latimer RD, Nordlander M, Feneck RO (2003) Comparison of clevidipine with sodium nitroprusside in the control of blood pressure after coronary artery surgery. Eur J Anaesthesiol 20:697-703
20. Hearse DJ, Bolli R (1992) Reperfusion induced injury: manifestations, mechanisms, and clinical relevance. Cardiovasc Res 26:101-108
21. Lefer AM, Lefer DJ (1996) The role of nitric oxide and cell adhesion molecules on the microcirculation in ischemia-reperfusion. Cardiovasc Res 32:743-751
22. Moncada S, Palmer RM, Higgs EA (1991) Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol Rev 43:109-142
23. Ohlmann P, Martinez MC, Schneider F, Stoclet JC, Andriantsitohaina R (1997) Characterization of endothelium-derived relaxing factors released by bradykinin in human resistance arteries. Br J Pharmacol 121:657-664
24. Lefer DJ, Nakanishi K, Johnston WE, Vinten-Johansen J (1993) Antineutrophil and myocardial protecting actions of a novel nitric oxide donor after acute myocardial ischemia and reperfusion in dogs. Circulation 88:2337-2350
25. Hearse DJ (1998) Myocardial protection during ischemia and reperfusion. Mol Cell Biochem 186:177-184
26. Gourine AV, Pernow J, Poputnikov DM, Sjoquist PO (2002) Calcium antagonist clevidipine reduces myocardial reperfusion injury by a mechanism related to bradykinin and nitric oxide. J Cardiovasc Pharmacol 40:564-570
27. Berkels R, Egink G, Marsen TA, Bartels H, Roesen R, Klaus W (2001) Nifedipine increases endothelial nitric oxide bioavailability by antioxidative mechanisms. Hypertension 32:240-245
28. Kitakaze M, Node K, Minamino T, Asanuma H, Kuzuya T, Hori M (1999) A Ca channel blocker, benidipine, increases coronary blood flow and attenuates the severity of myocardial ischemia via NO-dependent mechanisms in dogs. J Am Coll Cardiol 33:242-249
29. Kitakaze M, Asanuma H, Takashima S, Minamino T, Ueda Y, Sakata Y, Asakura M, Sanada S, Kuzuya T, Hori M (2000) Nifedipine-induced coronary vasodilation in ischemic hearts is attributable to bradykinin- and NO-dependent mechanisms in dogs. Circulation 101:311-317
30. Gobbel GT, Chan TY, Chan PH (1997) Nitric oxide- and superoxide-mediated toxicity in cerebral endothelial cells. J Pharmacol Exp Ther 282:1600–1607
31. Braunwald E, Kloner RA (1985) Myocardial reperfusion: a double-edged sword? J Clin Invest 76:1713-1719
32. Jalowy A, Schulz R, Dorge H, Behrends M, Heusch G (1998) Infarct size reduction by AT1-receptor blockade through a signal cascade of AT2-receptor activation, bradykinin and prostaglandins in pigs. J Am Coll Cardiol 32:1787-1796
33. Gourine A, Gonon A, Sjoquist PO, Pernow J (2001) Short-acting calcium antagonist clevidipine protects against reperfusion injury via local nitric oxide-related mechanisms in the jeopardised myocardium. Cardiovasc Res 51:100-107
34. Stephens CT, Jandhyala BS (2002) Effects of fenoldopam, a dopamine D-1 agonist, and clevidipine, a calcium channel antagonist, in acute renal failure in anesthetized rats. Clin Exp Hypertens 24:301-313
35. Hayashi K, Wakino S, Homma K, Sugano N, Saruta T (2005) Pathophysiological significance of T-type Ca2+ channels: role of T-type Ca2+ channels in renal microcirculation. J Pharmacol Sci 99:221-227