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Clevidipine in Cardiac Surgery: A Literature Review

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Abstract

Clevidipine is a dihydropyridine calcium channel blocker, with a pharmacokinetics and pharmacodynamics that make him unique. It is indicated for the reduction of blood pressure when oral therapy is not feasible or not desirable and has been widely used in the perioperative context. One of the most important uses is in cardiac surgery. Several studies suggest clevidipine as a safe, cost effective alternative to sodium nitroprusside (NTP) for treatment of acute aortic syndromes. Since this drug's approval, it has been studied in the preoperative and postoperative setting of cardiac surgery (such as valve replacement, reparation or in/off pump coronary artery bypass grafting). Not so common Merry et al. describes its use in the intraoperative setting, but focusing in the pre-pump lapse. Besides, Tobias et al. is the only one who apparently describes its use during the pump, suggesting that due to its mechanism of action, clevidipine may not be effective to reduce the in-pump hypertension due to hypothermia. Moreover, clevidipine has been related to cardio protection because of its interference in the mechanisms of ischemia-reperfusion. These findings are inconsistent, as the evidence is contradicting. It has only been studied in porcine models. The reason for this review is the need to clarify whether to use clevidipine before, after or even during the extracorporeal circulation depending on the evidence to date.

Keywords: Clevidipine; Cardiac surgery; Dihydropyridine

Introduction

Clevidipine is a non-dihydropyridine calcium channel blocker approved by the FDA in 2008 for the reduction of blood pressure (BP) when oral therapy is not feasible or not desirable. In 2011 the EMA authorized clevidipine for the rapid reduction of BP in the perioperative setting. Several intravenous (IV) drugs are available for this use, however clevidipine is characterized by a unique pharmacokinetic and pharmacodynamic profile. It has a rapid onset and offset of action and exerts a selective arteriolar vasodilation effect that results in the rapid reduction of systemic vascular resistance (SVR) without affecting neither the preload nor cardiac contractility [1-4]. The peri- operative setting of cardiac surgery represents a clinical condition that requires a precise BP control with minimal risk of non-expected hypotension, which might reduce the perfusion of vital organs. The rapid onset and offset of action of clevidipine allow for a precise BP control without BP excursions above or under de desire BP range. Our review examines the available evidence on the use of clevidipine in cardiac surgery.

Pharmacokinetics

Distribution and elimination

The offset of clevidipine action is fast and essentially depends on its distribution, which follows a two-compartment model, in which the half-life of the initial phase is 1 minute and the half-life in the terminal phase lasts 15 minutes. The clearance is very high (0.121 l/min/kg) and the volume of distribution is low (0.17 l/kg). In most patients, full recovery of blood pressure is achieved in 5-15 minutes after the infusion is stopped. The clearance is even lower in a state of hypothermia compared to normothermia. However, the drug effectively controls BP before and during hypothermic cardiopulmonary bypass surgery [5]. The context-sensitive half-life of clevidipine (50% reduction following completion of perfusion) is less than 1 minute, regardless of the infusion duration or the total administered dose. The time to reach a 90% reduction of plasma levels is approximately 5 minutes. Clevidipine has a high plasma protein binding (around 99.7%), and 15% of the drug and its inactive metabolites are excreted in faces [6].

Metabolism

Clevidipine is metabolized through rapid hydrolysis to hemiacetal ester and butyric acid by esterases in the blood and extravascular tissues. Thereafter the hemiacetal ester is converted into the main metabolite (pharmacologically inactive) which further undergoes glucuronidation, oxidation and decarboxylation, before being excreted in urine and faeces. The initial and terminal half-life is of 1 minute and approximately 9 hours, respectively. It is unlikely that kidney and liver dysfunction might affect the pharmacokinetics of clevidipine, thus no dose- adjustment is required in patients with liver or kidney impairment.

Pharmacodynamics

Clevidipine exerts a dose-dependent decrease in systemic vascular resistance and BP- lowering effect within 2 minutes after starting the infusion. It does not affect cardiac filling pressure (pre-load) nor reduces neither the central venous pressure (CVP), nor pulmonary capillary pressure (PCP) or cardiac contractility. It causes a dose-dependent increase in systolic volume due to the reduction of the afterload. There may be a slight dose-dependent increase in heart rate, less pronounced than that observed with sodium nitroprusside (SNP) [7,8]. After the infusion is stopped baseline BP values are recovered in a period of 2-5 minutes. High doses of clevidipine cause coronary dilation and a decrease of myocardial oxygen consumption, which improves the balance of myocardial oxygen delivery and extraction [9].

Acute Aortic Syndromes

The term acute aortic syndrome (AAS) includes pathophysiological entities such as aortic dissection (AD), intramural hematoma and symptomatic aortic ulcer. According to the Stanford classification, aortic dissections may be divided into the following types:

Type A: Aortic dissection: this condition represents an emergency when diagnosed and early treatment is crucial, considering that it is associated with a mortality rate that increases by 1%-2% every hour after the onset of symptoms.

The goal of surgery is to prevent the occurrence of complete rupture, cardiac tamponed, acute myocardial infarction (AMI), cerebral hypo perfusion and other potential consequences. The mortality rate increases by more than 50% with every month without surgical intervention [10].

Type B: Aortic dissections: these should be addressed with medical treatment, as well as endovascular treatment in those cases with disease progression.

Medical treatment for both types should be aimed at achieving a drop in cardiac contractility (dP/dt) followed by subsequent management of afterload to delay disease progression. Hemodynamic objectives should be to achieve a systolic blood pressure (SBP) < 100 mmHg and a heart rate < 60 bpm [10]. Beta-blockers (BBs) are the first-line drug option as they cause the reduction of cardiac contractility, heart rate and SBP. However, BBs do not always allow to achieved SBP control and other antihypertensive drugs should be concomitantly administered. SNP has classically been used as the vasodilator of choice in acute aortic syndromes. SNP has a very rapid onset and offset and it can be rapidly titrated during the post-operative period. However, it does not exert a predictable dose–effect, which may result in unwanted acute hypotensive events. It has a dual mechanism of action through both venous and arterial dilation and reduces both preload and afterload. Finally, due to its metabolism, it can cause cyanide toxicity and methemoglobinemia. Its price has risen in the United States to 800 USD, which has generated the need to look for alternative drugs that allow for a more efficient use of sanitary resources. On this regard, Cruz et al [11]. Reported favourable clinical and pharmaco-economic results of a cost-effectivity study on the sanitary impact of replacing SNP by clevidipine. Two studies reported on the use of clevidipine for the treatment of AAS: Ulici et al [12] and Alviar et al [13]. Both were retrospective observational studies that reported on the clinical experience with the use concomitant use of clevidipine and esmolol in acute aortic dissection compared to concomitant SNP and esmolol. The first mentioned study included n = 14 cases (8 patients treated with clevidipine and 6 treated with SNP) and the second study communicated the results of a larger sample (n= 135 patients; 85 treated with SNP and 50 with clevidipine). The primary outcome of effectiveness was the SBP below the target value. The results suggested that clevidipine in combination with esmolol may have better cost-effectiveness than SNP in

treating acute aortic dissection, without increasing the risk of clinical adverse Although the evidence on the use of clevidipine in acute aortic syndromes remains limited, clevidipine could be proposed as an effective alternative to conventional iv treatments in this type of surgical procedure based on its pharmacokinetic and pharmacodynamic profile.

Planned Cardiac Surgery

The preoperative management and optimization of BP in patients undergoing cardiac surgery is one of the main objectives, taking into account that it has been demonstrated that perioperative hypertension increases the risk of the occurrence of acute myocardial infarction (AMI), stroke, and neurocognitive dysfunction and bleeding. The efficacy and safety of clevidipine for BP management in the perioperative setting of cardiac surgery, bypass or valve replacement, was investigated in the ESCAPE 1 and ESCAPE 2 clinical trials. Levy et al [14]. Investigated the efficacy and safety of clevidipine versus placebo with the possible addition of a bailout IV antihypertensive drug in the pre-operative period of n = 152 patients with SBP ≥ 160 mm Hg undergoing cardiac surgery. The protocol considered a target SBP reduction of ≥ 15% compared to baseline BP values during the first 30 minutes of clevidipine infusion. The results demonstrated that the target SBP was achieved at a median time of 6 minutes in the patients treated with clevidipine. Singla et al [15]. Reported the results of the ESCAPE 2 study, carried out in n = 206 patients with SBP ≥ 140 mmHg undergoing cardiac surgery and treated with clevidipine versus placebo with the possible addition of a bailout IV antihypertensive drug, in the post- operative period. The protocol considered a target SBP reduction of ≥ 15% compared to baseline BP values d and during the first 30 minutes of clevidipine. And the results demonstrated that this target was achieved at a median time of 5 minutes of the clevidipine infusion. The ECLIPSE study [16]. Was an open-label, randomised clinical trial conducted in 3 parallel groups which compared clevidipine to nicardipine (NIC), nitroglycerin (NTG) and SNP, respectively, in a total of n= 1,512 patients candidates to undergo cardiac surgery (coronary bypass or valve replacement) at 61 sites in the United States. Safety was the primary combined outcome of the study and was defined as the occurrence of death, stroke, myocardial infarction (MI) and kidney dysfunction. The results demonstrated a similar rate in patients treated with clevidipine compared to the 3 comparators, except of the individual component of mortality after 30 days, which was significantly higher in those patients who had been treated with SNP versus clevidipine (p = 0.04). The ECLIPSE study also investigated the efficacy of the 3 parenteral antihypertensive drugs in achieving and maintaining a precise BP control within a pre-specified target range. This was measured by the integral of the cumulative area under the curve (AUC) of SBP. This outcome represents the magnitude and duration of BP excursions above or below a predefined SBP range and. the results demonstrated a significantly lower AUC in those treated with clevidipine compared to SNP (p = 0.003) and to NTG (p = 0.0006). These results highlight the s potential of clevidipine to achieve and maintain a desired BP range and to reduce the occurrence of BP excursions, as both hypertension and hypotension events were associated with an increased risk of morbidity and mortality. The incidences of atrial fibrillation (AF) and sinus tachycardia were similar across the three treatment groups. Subsequently, Aronson and Levy [17]. Analyzed the ECLIPSE studies and considered the following pharmaco-economic outcomes: duration of surgery, time to extubation, number of days of in-hospital stay at the critical care unit and duration of total in- hospital stay. The results demonstrated that a precise SBP control and the reduction of BP excursions above or below the desired range (AUC ≤ 10 mmHg x min/h) leads to better use of healthcare resources by the reduction of time spent on mechanical ventilation and in-hospital stay duration, in patients undergoing cardiac surgery. The least available evidence on the use of clevidipine is in the intraoperative setting. Merry et al [18]. Compared the treatment with clevidipine to nitroglycerine in a double- blind, randomised study with n=100 patients undergoing bypass surgery and demonstrated that clevidipine was not inferior to NTG for the pre and intra- BP control (before extracorporeal circulation (ECC), in candidate patients for CABG. The primary outcome of efficacy was similar to that of the ECLIPSE study. The authors concluded that clevidipine was not inferior to NTG and is a safe alternative to NTG for a precise BP control before cardiopulmonary bypass grafting (CPB). Tobias et al [19]. Communicated the results of the so far only case-based report on the use of clevidipine in pediatric patients undergoing cardiac surgery to repair congenital heart disease (aortic coarctation, tetralogy of Fallot, atrial septal defect and ventricular septal defect). The authors reported that that clevidipine enabled good pre-and post- operative BP control. Two studies reported on the use of clevidipine during extracorporeal circulation provided contradictory results. The publication by Vuylsteke et al [20]. Reported on an analysis of the clevidipine metabolization during ECC, in patients who undergo a cardiopulmonary bypass (CPB). It proposes that, like remifentanil and esmolol, metabolization during hypothermia associated with ECC probably decreases plasma clearance of clevidipine, thus reducing the necessary dose of the drug. Although it was not included in the study objective, the authors stressed the point that clevidipine may provide suitable blood pressure management during ECC. The second, the above- mentioned publication by Tobias et al. Regarding pediatric patients, suggests that clevidipine is not a

good drug for the management of MAP during hypothermia in ECC, although the number of cases included in the study was very limited (n = 3). In those cases, MAP was suitably managed with sodium nitroprusside or phentolamine. The setting in which the bulk of the evidence on the safety and efficacy of the use of clevidipine has been gathered is the post-operative setting. There have been reports of dose-seeking studies in the post-operative period [21]. As well as comparative studies with SNP [22]. Which clevidipine was used safely with good efficacy results. These results may be added to the results of the above-mentioned ECLIPSE study [15-23].

Ischaemia-Reperfusion Injury

Few studies carried out in animal models have provided contradictory results on the decrease of ischaemia-reperfusion injury. The authors hypothesized that the protection against ischaemia-reperfusion injury may be due to the release of nitric oxide (NO) from coronary microcirculation and the decrease in myocardial oxygen consumption through release of NO mediated by bradykinin [26-28].

Conclusions

Clevidipine is a drug used for BP management in the peri-operative setting with satisfactory results. Although its clinical development has been carried out in cardiac surgery, its pharmacokinetic and pharmacodynamic profile render it a good alternative to SNP or NTG for achieving and maintaining BP in a desired range in those surgical procedures that require a precise hemodynamic control. In patients with acute hypertension during ECC clevidipine allows for a rapid and precise BP reduction by causing a selective SVR reduction without affecting venous capacitance, maintaining adequate cardiac output and venous return and thus ensuring the perfusion of vital organs. The evidence of this benefit of clevidipine in cardiac surgery has essentially been generated in patients undergoing coronary bypass or valve replacement surgery. In acute aortic syndromes, clevidipine has been safely used with satisfactory clinical outcomes at several centers, although the data-analysis has been retrospective. Thus, no specific recommendation could be done for its use in this mentioned surgical procedure.

References

1. Tulman DB, Stawicki SPA, Papadimos TJ, Murphy CV, Bergese SD. Advances in management of acute hypertension: a concise review. Discov Med. 2012; 13: 375-383.
2. Rivera A, Montoya E, Varon J. Intravenous clevidipine for management of hypertension. Integr Blood Press Control. 2010; 3: 105-111.
3. Smithburger PL, KaneGill SL, Nestor BL, Seybert AL. Recent advances in the treatment of hypertensive emergencies. Crit Care Nurse. 2010; 30: 24-30.
4. Varon J, Marik PE. Perioperative hypertension management. Vasc Health Risk Manag. 2008; 4: 615-627.
5. Nordlander M, Sjöquist PO, Ericsson H, Rydén L. Pharmacodynamic, pharmacokinetic and clinical effects of clevidipine, an ultrashort-acting calcium antagonist for rapid blood pressure control. Cardiovasc Drug Rev. 2004; 22: 227-250.
6. Ericsson H, Bredberg U, Eriksson U, Mellgård JÅ, Nordlander M, Regårdh CG, et al. Pharmacokinetics and arteriovenous differences in clevidipine concentration following a short- and a long-term intravenous infusion in healthy volunteers. Anesthesiology. 2000; 92: 993-1001.
7. Ericsson H, Fakt C, Mellgård JA, Nordlander M, Sohtell L, Regardh CG, etal. Clinical and pharmacokinetic results with a new ultrashort-acting calcium antagonist, clevidipine, following gradually increasing intravenous doses to healthy volunteers. Br J Clin Pharmacol. 1999; 47: 531-538.
8. Kotrly KJ, Ebert TJ, Vucins E, Igler FO, Barney JA, Kampine JP. Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. Anesthesiology. 1984; 60: 173-179.
9. Kieler-Jensen N, Jolin-Mellgård A, Nordlander M, Ricksten SE. Coronary and systemic hemodynamic effects of clevidipine, an ultra-short-acting calcium antagonist, for treatment of hypertension after coronary artery surgery. Acta Anaesthesiol Scand. 2000; 44: 186-193.
10. Tsai TT, Nienaber CA, Eagle KA. Acute Aortic Syndromes. 2005.
11. Cruz JE, Thomas Z, Lee D, Moskowitz DM, Nemeth J. therapeutic interchange of clevidipine for sodium nitroprusside in cardiac surgery P T. 2016; 41: 635-639.
12. Ulici A, Jancik J, Lam TS, Reidt S, Calcaterra D, Cole JB, et al. Clevidipine versus sodium nitroprusside in acute aortic dissection: A retrospective chart review. Am J Emerg Med. 2017; 35: 1514-1518.
13. Alviar CL, Gutierrez A, Cho L, Krishnaswamy A, Saleh A, Lincoff A. Clevidipine as a therapeutic and cost- effective alternative to sodium nitroprusside in patients with acute aortic dissection. Eur Hear J Acute Cardiovasc Care. 2017.
14. Levy JH, Mancao MY, Gitter R, Kereiakes DJ, Grigore AM, Aronson S, et al. 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-1. Anesth Analg. 2007; 105: 918-925.
15. Singla N, Warltier DC, Gandhi SD, Lumb PD, Sladen RN, Robert N, et al. Treatment of acute postoperative

hypertension in cardiac surgery patients: An efficacy study of clevidipine assessing its postoperative antihypertensive effect in cardiac surgery-2 (ESCAPE-2), a randomized, double-blind, placebo-controlled trial. Anesth Analg. 2008; 107: 59-67.

16. Aronson S, Dyke CM, Stierer KA, Dyke CM, Stierer KA, Levy JH, et al. The eclipse trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. Anesth Analg. 2008; 107: 1110-1121.
17. Aronson S, Levy JH, Lumb PD, Fontes M, Wang Y, Crothers TA, et al. Impact of perioperative blood pressure variability on health resource utilization after cardiac surgery: an analysis of the ECLIPSE trials. J Cardiothorac Vasc Anesth. 2014; 28: 579-585.
18. Merry AF, Avery EG, Nussmeier NA, Playford HR, Warman GY, Wang Y, et al. Clevidipine compared with nitroglycerin for blood pressure control in coronary artery bypass grafting: a randomized double-blind study. Can J Anesth Can d'anesthésie. 2014; 61: 398- 406.
19. Tobias JD, Schechter WS, Phillips A, Weinstein S, Michler R, Berkenbosch JW , et al. Clevidipine for perioperative blood pressure control in infants and children undergoing cardiac surgery for congenital heart disease. J Pediatr Pharmacol Ther. 2011; 16: 55-60.
20. Vuylsteke A, Milner Q, Ericssonr H, Mur D, Dunning J, Mellgård MJ, et al. Pharmacokinetics and pulmonary extraction of clevidipine, a new vasodilating ultrashort-acting dihydropyridine, during cardiopulmonary bypasst. 2000; 85: 683-689.
21. Bailey JM, Lu W, Levy JH, Ramsay JG, Lesserson LS, et al. Clevidipine in adult cardiac surgical patients: a dose-finding study. Anesthesiology. 2002; 96: 1086-1094.
22. Powroznyk AVV, Vuylsteke A, Naughton C, Misso SL, Holloway J, Mellgård J, et al. Comparison of clevidipine with sodium nitroprusside in the control of blood pressure after coronary artery surgery. Eur J Anaesthesiol. 2003; 20: 697-703.
23. Freiberger NA, Tellor KB, Stevens AM. Comparison of clevidipine versus sodium nitroprusside for the treatment of postoperative hypertension in cardiac Surgery patients. Hosp Pharm. 2016; 51: 461-467.
24. Aronson S, Dasta JF, Levy JH, Lumb PD, Fontes M, Wang Y, et al. A cost analysis of the impact of a new intravenous antihypertensive in managing perioperative blood pressure during cardiac surgery. Hosp Pract. 2014; 42: 26-32.
25. Segawa D, Sjöquist PO, Wang QD, Gonon A, Nordlander M, Rydén L, et al. 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. 2000; 36: 338-343.
26. Wang QD, Segawa D, Ericsson H, Sjöquist P, Johansson L, Rydén L, et al. Time-dependent cardioprotection with calcium antagonism and experimental studies with clevidipine in ischemic- reperfused pig hearts: part I. J Cardiovasc Pharmacol. 2002; 40: 228-234.
27. Gourine A, Gonon A, Sjöquist PO, Pernow J. Short-acting calcium antagonist clevidipine protects against reperfusion injury via local nitric oxide-related mechanisms in the jeopardised myocardium. Cardiovasc Res. 2001; 51: 100-107.
28. Odenstedt J, Månsson C, Grip L. Failure to demonstrate myocardial protective effects of the ultra short acting calcium antagonist clevidipine in a closed-chest reperfusion porcine model. J Cardiovasc Pharmacol. 2004; 44: 407-415.