

Research Article

Revisiting Clevidipine Experience in the Pediatric Population: a Perioperative Perspective

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ABSTRACT

Clevidipine is an intravenous calcium channel antagonist of the dihydropyridine class that acts primarily as a vasodilator of the arterial bed. During pediatric surgeries, boluses from 10 to 20 mcg/kg and infusions from 0.5 to 5 mcg/kg/min have been used for the treatment of hypertension or when controlled hypotension is required. Clevidipine's fast metabolism allows a precise titration of drug if higher or lower doses are required. Future prospective clinical trials will provide further knowledge regarding clevidipine's safety profile in pediatric patients.

Keywords: Clevidipine, Pediatric Surgery, Controlled Hypotension, Perioperative, Hypertension, Calcium Antagonist.

Introduction

Blood pressure management in the pediatric population is mandatory during perioperative hypertensive episodes or during controlled hypotension protocols.[1,2] There are several medications that can be used to achieve blood pressure control. Whether they are suitable or not for perioperative use relies on their pharmacological profiles.[3,4] Clevidipine is a dihydropiridine calcium channel blocker with an unspecific esterase, organ independent metabolism, and a very short half-life. Its performance proves equal to, if not better, than other medications used perioperatively for blood pressure control based on its precise titration and fast washout time.[5] Moreover, previous research reports a favorable safety profile when compared to other antihypertensive medications, such as direct vasodilators.[1] Since Tobias et al. published a review article in 2013, a prospective trial, and anecdotal case reports focused on this topic, there has been expanded use of this agent in the pediatric population. Available evidence from the literature was reviewed in order to present an updated analysis of clevidipine use in pediatric patients.

Clevidipine: Pharmacokinetic And Pharmacodynamic Properties

Clevidipine is an intravenous calcium channel antagonist of the dihydropyridine class that primarily acts as a vasodilator of the arterial bed [Figure 1].[5,6] It has been used for the treatment of perioperative hypertension and the induction of controlled hypotension. Clevidipine is rapidly hydrolyzed in the blood into a primary inactive metabolite. Subsequently this metabolite undergoes glucoronidation, oxidation or decarboxylation before it is excreted in urine and feces.[9] Clevidipine is hydrolyzed in a higher extent in whole blood than in plasma alone, possibly due to the more efficient hydrolyzing action of esterases located in the red blood cell membrane or the cytosol.[7] This results in a half-life of 1 to 3 minutes, thereby allowing easy titration by continuous intravenous administration.[5] Up to date evidence pertinent to this novel calcium channel antagonist has been focused on the perioperative hypertension management in adult population, although some authors have described its use in the pediatric population.

Ericsson et al. (2000) demonstrated a linear correlation between the dose rate and the concentrations of clevidipine in arterial blood at steady state in healthy male subjects.[8] A previous study by the same author found a lag time of about 0.5-1.0 minutes between the termination of clevidipine infusion and the start of rapid decrease in clevidipine concentrations in the blood.[7] However, some studies found that no lag time was present in arterial blood collected from patients that undergoing

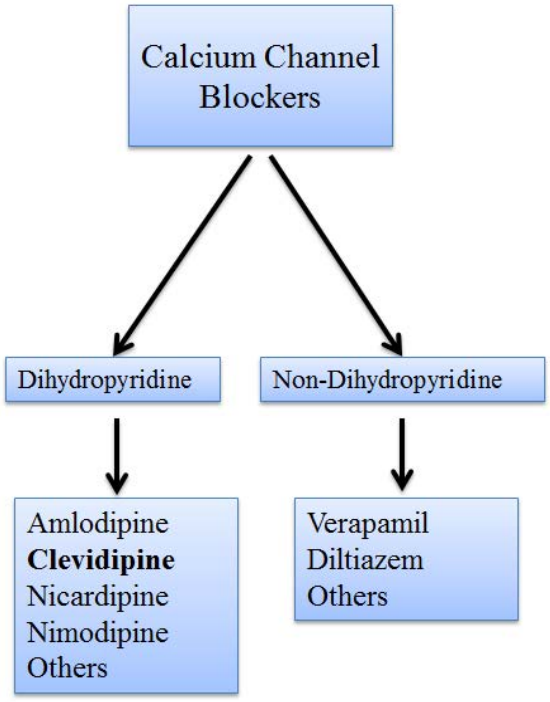

Figure 1: Calcium channel blocker classification.

coronary artery bypass grafting (CABG) surgery (9). Vuylsteke et al reported a statistically significant lower clearance of clevidipine in patients undergoing cardiopulmonary bypass (CPB).[10]

The pharmacodynamic effects of clevidipine have been demonstrated in different clinical trials. In healthy volunteers, clevidipine was administered as a continuous intravenous infusion at different time points and rates.[8,11,12] The results indicated that an infusion of 16 mcg/kg/min was well tolerated. A dose of 22 mcg/kg/min further reduced mean arterial pressure (MAP) by 10% and the heart rate (HR) reached the safety endpoint of 120 beats/minute, therefore, no further dose escalation was pursued.[12]

Studies performed in patients with essential hypertension showed a rapid decline of clevidipine's effect after infusion discontinuation. A stable HR was attributed to chronic oral treatment with β-adrenergic antagonists.[13] In a placebo-controlled clinical trial, clevidipine was titrated to predetermined infusion rates. The subjects were required to stop antihypertensive treatment for two weeks prior to participating in the study.[14] Clevidipine caused a dose-dependent reduction in blood pressure with a maximum decrease of 30% at the highest dose. A moderate increase in HR was attributed to the lack of β-blockers therapy. Clevidipine's effects on blood pressure ended once the infusion was stopped. [14]

Recent studies evaluated the clinical efficacy and safety of clevidipine use in anesthetized patients undergoing cardiac surgery.[9,10,13,15,16] Towe et al. demonstrated the efficacy of clevidipine BP control in the pediatric population.[17] A retrospective analysis was conducted in 10 pediatric patients ranging in age from 9 to 18 years. Perioperative hypertension was managed using clevidipine perioperatively in doses that ranged from 0.5 to 3.5 mcg/kg/min.

Based on the data published by Tobias et al., a bolus dose of clevidipine of 10 – 15 mcg/kg or an infusion of 1 – 5 mcg/kg/min was effective in the control of hypertension during emergence from anesthesia without causing excessive hypotension.[5] However, clevidipine was not effective in controlling MAP during CPB in the cooling phase, even when high doses were used. Calcium channels inactivation during hypothermia while on CPB, may prevent clevidipine's intended action.[5]

CLINICAL USE OF CLEVIDIPINE

Studies reporting clevidipine use in pediatric population are limited. These are summarized in Table 1.

III.1 Perioperative hypertension

Perioperative hypertension during surgery may lead to significant bleeding and suture line disruption, specifically during congenital heart disease (CHD) surgery.[1,5] Hypertension in children may be defined as a systolic blood pressure above the 95% percentile for gender, age and height.18 Management of intraoperative and postoperative hypertension must include the assessment of reversible causes, such as pain, agitation, hypoxemia, hypercarbia or sympathetic system activation.[1,5,19,20] Specific pharmacological treatment should only be attempted after managing reversible etiologies.[1,20]

Secondary causes of hypertension are more prevalent in children than in adults.[18] Renal vascular or parenchymal disease and volume overload can account for preoperative hypertension, as well as endocrine disease, obstructive sleep apnea, coarctation of the aorta, rheumatologic disease, and drug-induced hypertension.[18,19,21] Patients with pre-diagnosed hypertension may be more challenging to manage during surgery than non-hypertensive patients due to an exaggerated hemodynamic response.[19,21]

Several medications have been used to treat hypertension during or following pediatric surgery. Direct vasodilators, β-adrenergic antagonists, renin-angiotensin system inhibitors, and calcium antagonists are all available for this indication.[1] Clevidipine has been used as an antihypertensive medication in pediatric patients undergoing different surgical procedures from the preoperative to the postoperative period.[1,17,19,20] Available evidence is based on case reports and two retrospective studies [1, 5, 17, 21].

Clevidipine shows attractive pharmacokinetics, pharmacodynamics, and safety profile for perioperative use.[1,5,19]. Clevidipine's action on L-voltage regulated calcium channels of the smooth vascular muscle accounts for its predominant arterial vasodilator effect, with little or no effect on the venous system and cardiac preload. Furthermore, clevidipine has no direct chronotropic or inotropic effects on the myocardium. Altogether these pharmacological effects limit concerns regarding bradycardia, reflex tachycardia, severe hypotension, or effects on stroke volume.[1,5,19] However, in some studies β-adrenergic antagonists were required during infusion to control clevidipine induced reflex tachycardia.[17,21] Unlike sodium nitroprusside, there are no concerns of cyanide toxicity with clevidipine. It has been proven to be more effective than nitroglycerin and as effective as nitroprusside and nicardipine for blood pressure control. In 2008, Aronson et al reported an improved mortality

Table 1: Overview of studies using clevidipine for BP control in children.

Authors	Number of subjects	Type of study and patients demographics	Clevidipine dosing	Outcomes and conclusions
E. Towe and J. Tobias, 2009[17].	10	*Retrospective.* Patients between 9 - 18 years of age who received clevidipine for perioperative hypertension or to provide controlled hypotension (CH).	Infusion was started at 0.5-1 mcg/kg/min. Clevidipine dose was titrated up every 3 to 5 minutes as needed to a rate of 0.5-2 mcg/kg/min for hypertension vs 3-3.5 mcg/kg/min for CH.	Clevidipine was equally effective whether used to manage hypertension or for CH, although a larger dose was required to achieve CH.
J. Tobias and D. Hoernschemeyer, 2011[31].	20	*Retrospective.* Patients <18 years of age who received clevidipine for intraoperative CH during spinal surgery.	When MAP was ≥ 65 mmHg, a clevidipine infusion was started at 0.5-1 mcg/kg/min, and increased by 0.5-1 mcg/kg/min every 2 to 3 minutes to achieve the desired MAP of 50-65 mmHg.	The target MAP was achieved within 5 minutes in 15 of the 20 patients and returned to baseline within 5 minutes in 16 of the 20 patients.
J. Tobias *et al*, 2011[5].	14	*Retrospective.* Patients undergoing surgery for congenital heart disease (CHD), ranging in age from 11 months to 15 years.	Infusion started at 1 mcg/kg/min and increased by 0.5-1.0 mcg/kg/min as needed. During CPB, BP control was ineffective despite maximum dosing at 10 mcg/kg/min.	Clevidipine is effective for perioperative BP management in pediatric CHD surgery. Clevidipine it is not effective to control BP during CPB and cooling.
H. Kako *et al*, 2015[30].	30	*Prospective.* Patients undergoing posterior spinal fusion for neuromuscular scoliosis, ranging in age from 7.9 to 17.4 years, requiring CH at an MAP of 55-65 mmHg.	Initial clevidipine infusion initiated at 0.25-1 mcg/kg/min and titrated up in increments of 0.25-1 mcg/kg/min every 3 to 5 minutes to achieve the desired MAP.	More than half of the 30 patients (53.3%) achieved the target MAP within 5 minutes. When the clevidipine infusion was discontinued, the MAP returned to ≥ 65 mmHg within 10 minutes in 12 of the 30 patients (40.0%).

associated with clevidipine when compared to nitroprusside for BP control in cardiac surgery patients.[22]

Hemodynamic management has been successfully achieved with clevidipine during aortic coarctation surgery and congenital heart disease.[1,5] The recommended dose for blood pressure control in adults ranges from 0.4 to 8 mcg/kg/min. However, the highest range doses should not be maintained for more than 2 hours.[19] A starting infusion between 1-5 mcg/kg/min has been used during coarctation of the aorta surgery.[1] Doses as low as 0.5 mcg/kg/min have been used during hernia repair, peritoneal catheter placement, or pheochromocytoma surgery.[19,21] A 10-20 mcg/kg bolus can be used for prompt blood pressure control.[1] Bettesworth et al reported pheochromocytoma resection under clevidipine infusion for blood pressure control. Even though satisfactory blood pressure management was achieved, heart rate response was not adequately controlled by clevidipine, requiring β-adrenergic antagonist administration.[21] Tobias et al concluded that clevidipine is effective for perioperative BP control in cardiac surgery, except during cardiopulmonary bypass and hypothermia.[21]

Given its short half-life, and its fast organ-independent metabolism, titration is rapidly achieved if higher or lower doses are required (median of 6 min in the adult population), as opposed to nicardipine which has a long half-life.[20] Evidence shows that clevidipine has a better performance than nicardipine when tight BP control is needed, making clevidipine a valuable option for the management of hypertensive urgencies and emergencies.[19,21] There is no rebound hypertension effect described after discontinuation of clevidipine and transition to other antihypertensive medications.[1,19]

Each clevidipine vial contains 25 mg in a 50 mL lipid solution, and drug administration errors can occur due to similarities with propofol vials.[1,21] The cost of each vial is approximately $50-$70.[21] Its use should potentially be avoided in patients with true egg or soy allergies (anaphylaxis) and in patients with lipid metabolism disorders.[1,20,21] In relation to its pharmaceutical presentation, mild elevation of triglycerides has been shown in children when clevidipine was administered with propofol.[1]

The original formulation did not include a bacteriostatic

component, therefore, the used vial should be discarded within 4 hours of product administration to avoid bacterial contamination.[1] Bacterial growth is still a concern, and new formulation includes EDTA disodium, extending the product lifetime up to 12 hours after the vial is open as long as strict aseptic technique is followed during administration.[20]

III.2 Controlled hypotension

Controlled hypotension (CH) requires the use of a medication to induce the reduction of BP to a targeted range and in a specific time during the procedure. This method is used during surgery to limit blood obscuring vision in the operative field, and when a significant blood loss is expected. The target pressure for CH can vary. A reduction of BP to a systolic value of 80–90 mmHg, mean arterial pressure (MAP) of 50–65 mmHg, or a decrease of 30% from baseline MAP is considered clinically acceptable.[2]

In pediatric surgery, the advantage of improving the surgical field vision, plus the potential reduction on blood product transfusion requirements, make this technique a compelling tool. Nevertheless, the potential risk for excessive hypotension raises concerns regarding insufficient e nd-organ perfusion pressure and consequent damage. It is important to closely monitor BP during CH generally with an indwelling arterial cannula. It should be induced only for as short period of time as required, to minimize the risk of impaired organ perfusion.[4]

Various medications have been used for CH in adults.[2] However, when considering the pediatric-aged population, the studies are limited. Sodium nitroprusside, a direct vasodilator, has been widely used for CH in children.[23,24] Other vasodilators have also been used including fenoldopam or nicardipine, as well as the α-2-adrenoceptor agonists dexmedetomidine or clonidine. [3,25-27] Anesthetic agents, including sevoflurane and remifentanil may also be effective when a reduction of MAP is desired.[28,29]

To date, limited studies have evaluated the effectiveness of clevidipine in pediatric surgeries when CH is required. Pharmacologic characteristics of clevidipine, such as a rapid onset and a short clinical half-life, make this medication an attractive option for CH induction.[20] Drug administration by infusion can be easily adjusted during CH. For the initial infusion rate dose, a minimum of 0.25 mcg/kg/min or 0.50 mcg/kg/min, with a maximum of 5 mcg/kg/min can be used. Sequential increments in the infusion dose every 2 to 3 minutes, until the targeted MAP is achieved, have been shown to be effective.[30,31] The combination of bolus dosing (10-20 mcg/kg) and a titrated infusion are also effective for targeting and maintaining the desired MAP during CH.[1,32] Clevidipine can be rapidly titrated along with changes in levels of sympathetic stimulation.[31]

SAFETY AND TOXICITY

Calcium channel antagonists carry the risk for excessive hypotension, negative inotropic effects and cardiac conduction anomalies as possible adverse events (AEs).[19] However, clevidipine has shown a promising safety profile in the pediatric and adult population, similar to nicardipine. In addition, due to its short half-life, the titration of the infusion can promptly reverse related AEs.[9,17,19,20,30,31,33,34]

The package insert of clevidipine describes headache (6.3%), nausea (4.8%), chest discomfort (3.2%) and vomiting (3.2%) as the most common AEs; most of these AEs were observed during the pivotal phase III clinical trials, with no statistical significance from placebo.[30-35] Furthermore, excessive hypotension and reflex mild tachycardia (≥20% increase in heart rate) are described as potential events of rapid upward titration of this medication.[5,17,20,30,33]

The literature does not describe pharmacological AEs of clevidipine on the respiratory, hepatic endocrine systems, and coagulation pathways; however, some authors reported elevated serum triglyceride levels with no clinical consequences (≥150 mg/dl). Excessive hypotension (MAP ≤ 50 mm Hg) remains the most common (2%) AE requiring clevidipine discontinuation while the administration of a β-adrenergic antagonist may be required for tachycardia.[17,19,31] In addition, several studies with clevidipine and placebo administration describe other AEs including, but not limited to, acute renal failure, atrial fibrillation, myocardial infarction, syncope, dyspnea, sinus tachycardia, polyuria and flushing. However there were no statistical differences between clevidipine and placebo when considering the AE profiles.[19,20,33,35]

FUTURE DIRECTIONS IN RESEARCH

Clevidipine is FDA approved for treating hypertension in adults when oral administration is not feasible. Its use in children has been reported in patients as young as 11 months of age.[5] However, caution should be advised with use in infants and neonates until more research is conducted.[1,20] Future clinical trials are needed to describe the characteristics, efficacy and safety of clevidipine in children.

A prospective, open-label study to evaluate the feasibility of administering clevidipine infusion for a minimum of 30 minutes and up to a maximum of 96 hours in pediatric patients undergoing a surgical procedure for which intravenous antihypertensive therapy is expected (www.clinicltrials.gov; NCT01938547), is currently under recruitment of subjects.

CONCLUSIONS

Clevidipine is an effective agent to manage perioperative hypertension and provide controlled hypotension with an acceptable safety profile in children. Moreover, its fast metabolism prevents accumulation and allows a fast reversal of its action adapting to variable hemodynamic changes during surgery.

Conflict of Interest

The authors did not receive any funding and have no conflicts of interests related to this publication.

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