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Clevidipine for perioperative pressure control in a child with aortic coarctation

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Key points

1. Clevidipine is a dihydropyridine calcium channel antagonist with physiologic properties similar to nicardipine including vasodilation primarily of the arterial system with limited effects on the inotropic, chronotropic, and dromotropic (conduction) function of the myocardium.
2. Clevidipine undergoes rapid metabolism by tissue and plasma esterases resulting in an ultra-short half-life allowing it to be easily titrated by continuous infusion with a rapid resolution of its effects when the infusion is discontinued.
3. Clevidipine has been shown to be effective in the treatment of hypertension in various scenarios in the adult population including patients undergoing cardiac surgery.
4. Anecdotal experience suggests its efficacy in various clinical scenarios in the pediatric population including the perioperative period, in patients with hypertension related to renal disease, and following surgery for congenital heart disease.

Abstract

Clevidipine is a short-acting, intravenous calcium channel antagonist of the dihydropyridine class. Rapid metabolism by blood and tissue esterases results in a half-life of 1-3 minutes. We present anecdotal experience with the use of clevidipine to provide perioperative BP control in a 2-year-old child with aortic coarctation. Options for BP control in pediatric patients are discussed and previous reports of clevidipine use are reviewed.

Keywords: Clevidipine; hypertension, aortic coarctation, calcium channel antagonist

Introduction

Various factors may result in perioperative hypertension in the pediatric-aged patient including renal disease, volume overload, activation of the sympathetic nervous system, or alterations in the renin-angiotensin cascade.[1,2] Postoperative hypertension is particularly prevalent following surgery for aortic coarctation.[3] In such circumstances, blood pressure (BP) control is mandated as excessive hypertension may result in excessive bleeding or disruption of suture lines. After excluding treatable causes of hypertension including pain, hypercarbia, and hypoxemia, pharmacologic control of BP may be indicated.

Clevidipine (Cleviprex®, The Medicines Company, Parsippany, NJ 07054) is a short-acting, intravenous calcium channel antagonist of the dihydropyridine class.[4,5] Its most unique pharmacokinetic property is its ultra-rapid metabolism by blood and tissue esterases with a resultant half-life of 1-3 minutes. We present anecdotal experience with the use of clevidipine to provide perioperative BP control in a pediatric patient during repair of aortic coarctation. Options for BP control in pediatric patients are discussed and previous reports of clevidipine use are reviewed**.**

Case report

Approval for the publication of case reports involving a single patient is not required by the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). The patient was a 2.5 year old, 13.2 kg child presenting for repair of aortic coarctation. Pediatric cardiology consultation was prompted at 2 years of age for evaluation of a murmur. At that time, his physical examination was unremarkable except for a BP discrepancy (right arm: 102/68 mmHg; right leg: 84/42 mmHg). Subsequent cardiac MRI revealed aortic coarctation and a bicuspid aortic valve. His past medical history was negative. On the day of surgery, he was held *nil per os* for 6 hours and transported to the operating room where standard American Society of Anesthesiologists' monitors were placed. Following the inhalation induction of anesthesia with sevoflurane, two peripheral intravenous cannulae and a right radial arterial cannula were placed. Anesthesia was maintained with isoflurane and fentanyl. Prior to surgical incision, a caudal block was placed with 500 µg morphine and 10 µg clonidine. A left thoracotomy was performed and the aortic coarctation repaired using with an end-to-end anastomosis. Prior to the aortic cross-clamp clevidipine was titrated at 1-3 µg/kg/min to maintain the BP at 90-100/50-60 mmHg. The cross clamp time was 23 minutes. The clevidipine infusion was held for 2-3 minutes prior to release of the cross-clamp and then restarted to maintain the BP at 80-100/45-60 mmHg. No change in the heart rate was noted. At the completion of the case, the patient's trachea was extubated. He was transported to the Cardiothoracic ICU. During this time, the clevidipine was continued at 1-3 µg/kg/min to prevent hypertension. The next morning, he was transitioned to oral enalapril for BP control. The remainder of his postoperative course was uneventful.

Discussion

Several agents have been used to control perioperative blood pressure in infants and children including sodium nitroprusside (SNP), ß-adrenergic antagonists, calcium channel antagonists, and inhibitors of the renin-angiotensin system.[2] SNP is a potent, direct-acting vasodilator. Release of nitric oxide within the cytoplasm results in vasodilatation of venous and arterial vessels with an immediate onset and short half-life. SNP rapidly and predictably decreases the mean arterial pressure making it a popular option when rapid titration of BP is needed including the postoperative period. Despite this a recent open label trial in 153 pediatric patients demonstrated limited efficacy with SNP when used for controlled hypotension as the BP was within the desired range only 45.4% of the time.[6] Potential adverse effects of SNP include excessive hypotension even when used within recommended dosing guidelines or even cardiovascular collapse with overdosing. The risk of excessive hypotension as well as wide fluctuations in BP mandates intra-arterial blood pressure monitoring. Cyanide and thiocyanate toxicity may occur more commonly with prolonged dosing, high infusion rates, in the presence of hepatic or renal dysfunction, and in patients with a poor nutritional state.[7] Additional concerns include rebound hypertension when it is discontinued, cerebral vasodilatation with the potential to increase intracranial pressure, increase in intrapulmonary shunt, and dose-dependent alterations in platelet aggregation.[8] Reflex tachycardia frequently requires the addition of a second agent such as a β-adrenergic antagonist to control heart rate.

Labetolol exhibits selective competitive antagonist of the α_1 adrenergic receptor and non-selective blockade of

the $ß_1$ and $ß_2$-adrenergic receptors. These physiologic effects result in decreased systemic vascular resistance with control of HR. Following intravenous administration, BP effects occur within 2-5 minutes with a peak effect at 5-15 minutes. Previous reports have demonstrated its efficacy in the pediatric population albeit with a potentially longer time to achieve effect BP control.[9,10] Potential issues include a relatively prolonged duration of action (2-4 hours) and an adverse effect profile that includes bradycardia, heart block, depressed left ventricular function, and bronchospasm.

Esmolol is a short-acting, selective β_1-adrenergic receptor antagonist. Rapid metabolism by esterases results in rapid and effective titration by continuous infusion. In the adult population, esmolol has been used most commonly for heart rate or arrhythmia control in various clinical scenarios including unstable angina, myocardial ischemia, supraventricular arrhythmias, and perioperative tachycardia.[11] Its relative selectivity for the β_1-adrenergic system limits its effects on airway reactivity.[12] Previous studies have demonstrated its efficacy in controlling hypertension following surgery for aortic coarctation.[13,14] Although it has also been noted that dosing requirements to achieve such BP may be substantially higher (mean 700 µg/kg/min) than that used in adult patients.

Hydralazine is a direct systemic arterial vasodilator that activates guanylate cyclase to produce vasodilatation with clinical effects occurring in 10-20 minutes. It has a modest antihypertensive effect if used alone because of reflex tachycardia. Therefore, the concomitant administration of a β-adrenergic antagonist may be required. Given its longer duration of action, easy titration by continuous intravenous administration is not feasible. A recent retrospective review demonstrated that only 21% of the 110 patients achieved a ≥ 25% reduction of systolic or diastolic BP.[15]

Like clevidipine, nicardipine is a dihydropyridine, calcium channel antagonist.[16] Its physiologic effects result from the blockade of calcium entry into vascular smooth cells by modulation of L-type voltage gated calcium channels. Preferential vasodilation of the arterial versus the venous system is achieved thereby limiting reflex tachycardia. Several studies have demonstrated effective BP control in infants and children in various clinical scenarios including following surgery for congenital heart disease.[17-19] Although the risk of excessive hypotension is limited, its duration of action may be prolonged following a continuous infusion.

Clevidipine is an intravenous calcium channel antagonist of the dihydropyridine class which results primarily in vasodilatation of the arterial bed with limited effects on the inotropic and chronotropic function of the myocardium.[20,21] It was approved by United States Food & Drug Administration in August 2008 for use in adults for the reduction of blood pressure when oral therapy is not feasible. It is the only intravenous antihypertensive medication approved during the past 10 years. To date, the majority of experience with this novel calcium channel antagonist has been in the adult population in various clinical scenarios including cardiac surgery, neurosurgical procedures, intracerebral hemorrhage, and the postoperative period.[22-26]

When compared with other antihypertensive agents, preliminary data have suggested the potential superiority of clevidipine over other agents such as SNP or nitroglycerin. In a prospective trial comparing clevidipine with SNP, nitroglycerin or nicardipine for the treatment of acute hypertension in adult cardiac surgery patients, BP control was more effective with clevidipine when compared with nitroglycerin or SNP.[27] No difference was noted when compared to nicardipine. Of note, mortality was significantly decreased in patients receiving clevidipine than in patients receiving SNP (p=0.04).

When compared to SNP, the clinical benefits include less reflex tachycardia, limited effects on venous system without changes in preload, a decreased incidence of excessive hypotension, and no concerns regarding cyanide toxicity. In a recent trial evaluating the efficacy of

SNP in controlling BP in the pediatric population, fourteen of the patients (27%) had whole blood cyanide levels greater than 0.5 µg/mL although there were few clinical signs of cyanide toxicity.[28] When compared with β-adrenergic antagonists such as esmolol and labetolol, clevidpine has no effects on airway reactivity, does not decrease the chronotropic function of the conduction system, and does not have direct negative inotropic properties. In fact, as it dilates the arterial system and decreases systemic vascular resistance, cardiac output is generally increased.[29,30] In our patient, clevidipine in doses ranging from 1-3 µg/kg/min effectively controlled intraoperative BP during aortic cross-clamping. Additionally, its effects dissipated rapidly to allow BP to increase prior to the release of the cross-clamp thereby preventing hypotension. Following the procedure, clevidipine was restarted to control postoperative hypertension until the following morning when the antihypertensive regimen was shifted to the oral administration of enalapril.

Although relatively anecdotal, previous experience has demonstrated similar efficacy with clevidipine in the pediatric population (table 1).[31-37] No increase in serum triglyceride levels has been reported in adults during clevidipine administration; however, anecdotal data from the pediatric population has noted a mild elevation of triglyceride levels when clevidipine is administered with propofol. In addition to these issues, the phospholipids of the solution may support bacterial growth. The vials are single-use and should be changed at 4 hour intervals. To date, the youngest pediatric patient to receive clevidipine in published reports has been 11 months of age.[34] Although nicardipine has been used safely in the neonatal population with limited effects on myocardial contractility, given previous experience demonstrating the catastrophic effects of verapamil in neonates and infants, more clinical data is needed to demonstrating the safety of clevidipine in neonates and young infants.[38,39]

However, with these caveats in mind, the current clinical experience suggests that clevidipine may be an effective agent for perioperative BP control in children including following repair of aortic coarctation. Dosing requirements have generally from 1 to 5 µg/kg/min with the majority of patients responding in the range of 2-3 µg/kg/min. Given its rapid half-life, titration of the infusion is generally effective in providing BP control. Two reports have used bolus dosing of 10-20 µg/kg to achieve more rapid control.[34,36]

Authors and reference	*Patients demographics*	*Clevidipine dosing*	*Outcome*
Tobias JD et al.[31]	16-year-old, 57 kg adolescent with renal failure for urgent placement of a peritoneal dialysis catheter.	0.2-2 µg/kg/min	Clevidipine started preoperatively to control BP prior to anesthetic induction. Continued intraoperatively and then postoperatively. Postoperatively after administration of the patient's usual morning dose of amlodipine, the clevidipine infusion was discontinued.
Towe E et al.[32]	Cohort of 10 pediatric patients, ranging in age from 9 to 18 years.	Initiated at 0.5 to 1 µg/kg/min and titrated up to 3.5 µg/kg/min as needed.	Indications for clevidipine included control of perioperative hypertension, intraoperative CH, and to improve distal perfusion. The highest doses were required for CH. Intermittent doses of metoprolol were required to control reflex tachycardia in 2 patients.
Tobias JD et al.[33]	Cohort of 20 patients, ranging in age from 14 to 18 years.	Initiated at 0.5 to 1 µg/kg/min and increased in increments of 0.5 to 1 µg/kg/min every 2 to 3 minutes to achieve the desired MAP of 50 to 65 mm Hg.	Clevidipine was effective for CH in all patients. Mild tachycardia required use of a β-adrenergic antagonist in 4 of the 20 patients. A mild elevation in TG levels was noted in 3 of 6 patients when clevidipine was administered with propofol.
Tobias JD et al.[34]	Cohort of 14 patients with CHD ranging in age from 11 months to 15 years.	Continuous infusion was started at 1 µg/kg/min and increased in increments of 0.5 to 1 µg/kg/min	Clevidipine was effective for perioperative BP control in infants and children with CHD. It was ineffective during hypothermia while on CPB.
Butterworth JG et al.[35]	15-year-old adolescent with a pheochromocytoma.	Initiated at 0.5 µg/kg/min and titrated from 0.5 to 3 µg/kg/min to maintain the MAP within 20% of baseline. The infusion was continued at 0.5-1 µg/kg/min postoperatively.	Esmolol required to control tachycardia. After adrenalectomy, there were no abrupt changes in the hemodynamic parameters.
Croft K, and Probst S[36]	17-year-old, 50 kg adolescent for LeFort I osteotomy and mandibular osteotomy.	Following a bolus dose of 1 mg, the infusion was increased to 20 mg/hour that resulted in an immediate decrease of the MAP from 68 to 51 mmHg over 3 minutes.	Effective control of MAP to provide CH during the surgical procedure.
Kako H et al.[37]	Cohort of 30 patients, ranging in age from 7.9 to 17.4 years, requiring CH during posterior spinal fusion.	Infusion started at 0.25 to 1 µg/kg/min and titrated up in increments of 0.25 to 1 µg/kg/min every 3 to 5 minutes to achieve the desired MAP.	Clevidipine effectively provided CH during posterior spinal fusion. Both the onset and duration of action were rapid. Although titration of the infusion with occasional pauses were needed, excessive hypotension was not noted.

Table 1. Previous reports of clevidpine use in pediatric patients. BP = blood pressure; CH = controlled hypotension; MAP = mean arterial pressure; TG = triglyceride; CHD = congenital heart disease; CPB = cardiopulmonary bypass

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