Abstract

Introduction: Clevidipine is an ultra-short acting, intravenous calcium channel antagonist of the dihydropyridine class. Metabolism by blood and tissue esterases results in a half-life of 1-2 minutes thereby allowing easy titration by IV administration. We present preliminary experience with this novel agent to provide controlled hypotension (CH) in a cohort of adolescents undergoing posterior spinal fusion.

Methods: The records of patients ≤18 years of age who received clevidipine for CH were retrospectively reviewed. Demographic data included age, weight, gender, and co-morbid disease processes. Information regarding clevidipine included the initial infusion rate, time to achieve the target mean arterial pressure (MAP), the maintenance infusion rate, the average infusion rate, and the duration of administration. Hemodynamic information included the starting MAP and heart rate (HR) as well as the MAP and HR during the clevidipine infusion. Adverse effects related to clevidipine included excessive hypotension (need to discontinue the infusion or the need for a fluid bolus or administration of a vasopresor), tachycardia (20% increase in HR or the administration of a β-adrenergic antagonist) and elevated serum triglyceride level.

Results: The study cohort included 20 patients, ranging in age from 14 to 18 years and in weight from 46 to 96 kgs. To provide acceptable conditions for evoked potential monitoring, a total IV anesthetic technique was used. Propofol was started at 100 μg/kg/min and titrated to maintain the bispectral index at 40-60. Remifentanil was started at 0.1 μg/kg/min and increased up to 0.3 μg/kg/min as needed to control MAP. If the MAP was ≥65 mmHg, clevidipine was added to maintain the MAP at 50-65. The clevidipine infusion was started at 0.5-1 μg/kg/min and increased in increments of 0.5-1 μg/kg/min every 2-3 minutes to achieve the desired MAP. The target MAP was achieved within 5 minutes in 15 of the 20 patients and within 10 minutes in the other 5 patients. The maintenance infusion rate of clevidipine varied from 1-5 μg/kg/min (2.9 ± 0.7 μg/kg/min). With the administration of clevidipine, HR increased from a baseline of 76 ± 14 to 92 ± 11 beats/minute (p <0.05). The HR increase was ≥ 20 beats/minute in 4 patients. Intermittent doses of metoprolol were used in 3 patients to control the HR increase. No excessive hypotension was noted. A triglyceride level was drawn in 6 patients who received clevidipine with propofol and was elevated in 3 patients (≥150 mg/dL, high level 328 mg/dL). When the clevidipine infusion was discontinued, MAP returned to baseline within 5 minutes in 16 of the 20 patients and within 10 minutes in the other 4 patients.

Discussion: Clevidipine effectively controlled MAP and provided CH. Mild tachycardia was noted in
some patients with the occasional need for a β-adrenergic antagonist. No episodes of excessive hypotension were noted. Given its short half-life, clevidipine can be rapidly titrated to provide CH when changing levels of sympathetic stimulation may occur. Should inadvertent hypotension occur, its short duration of action offers an additional advantage over several other IV antihypertensive agents.

**Key words:** Clevidipine, calcium channel antagonist, controlled hypotension, spinal surgery

**Introduction**

Various techniques have been suggested as a means of limiting or avoiding the need for homologous blood transfusions. One such technique, controlled or deliberate hypotension (CH), involves the use of pharmacological agents to lower the mean arterial pressure (MAP) to 50-65 mmHg. Several different agents have been used to provide controlled hypotension including direct acting vasodilators (sodium nitroprusside, nitroglycerine), calcium channel antagonists (nicardipine), β-adrenergic antagonists, ganglion blocking agents, and the inhalational anesthetic agents.

Clevidipine (Cleviprex®, The Medicines Company, Parsippany, NJ 07054) is a short-acting, intravenous calcium channel antagonist of the dihydropyridine class. It undergoes rapid metabolism by non-specific blood and tissue esterases with a half-life of 1-3 minutes. It is currently approved by the Food & Drug administration for the reduction of blood pressure when oral therapy is not feasible or desirable. The majority of experience with this novel agent has been in the control of perioperative blood pressure in adults. There are only two reports regarding its use in pediatric-aged patients. We present our initial experience with clevidipine for CH during spinal surgery in adolescents.

**Methods**

These patients were cared for at the University of Missouri (Columbia, Missouri). This retrospective review and presentation of the data in this format were approved by the hospital’s Institutional Review Board. From the pharmacy database, patients who had received clevidipine for intraoperative CH during spinal surgery were identified. The following demographic data were obtained: age, weight, gender, and associated medical conditions. The intraoperative data included the anesthetic technique and agents used, duration of the surgical procedure, vertebral levels fused, estimated blood loss, fluids (including blood products) administered, and urine output. Information collected concerning clevidipine included the starting dose, time to achieve the desired MAP, mean infusion rate to maintain desired MAP, duration of the infusion, and the time to return of the MAP to baseline when the infusion was discontinued. The baseline heart rate and the maximum heart during the clevidipine infusion were recorded. Tachycardia was defined as a 20% increase in HR or the administration of a β-adrenergic antagonist. The intraoperative records were also reviewed for excessive hypotension defined as the need to turn off the infusion, the requirement for the administration of an adrenergic agonist (phenylephrine, ephedrine) or calcium, or the administration of a fluid bolus. When available, the triglyceride (TG) level obtained during the intraoperative infusion was noted. In the patients undergoing posterior spinal fusion, the baseline PaO₂ (prior to the start of clevidipine) and the lowest PaO₂ during the clevidipine infusion were recorded. Oxygenation data were collected only from patients undergoing posterior spinal fusion since it would have been difficult to determine whether alterations in oxygenation were related to the clevidipine infusion or the surgical procedure in patients undergoing thoracotomy, one-lung ventilation and
anterior spinal fusion. Statistical analysis included a paired t-test to determine the statistical significance of any increase in heart rate or decrease in PaO₂ from baseline after the start of the clevidipine infusion. All data are presented as mean ± SD.

Results

**DEMOGRAPHIC DATA:** The study cohort included 20 patients, ranging in age from 14 to 18 years and in weight from 46 to 96 kgs. There were 11 boys and 9 girls. Underlying medical conditions included idiopathic scoliosis (n = 11), neuromuscular scoliosis from cerebral palsy (n = 8), and Duchenne’s muscular dystrophy (n = 1).

**ANESTHETIC TECHNIQUE:** The patient was held nil per os for 6 hours and transported to the operating room where routine American Society of Anesthesiologists’ monitors were placed. Anesthetic induction consisted of either inhalation induction with increasing concentrations of sevoflurane in nitrous oxide/oxygen or intravenous induction with propofol (3-4 mg/kg). Following anesthetic induction, endotracheal intubation was facilitated by a single dose of rocuronium (0.4-0.6 mg/kg). Core body temperature was monitored using an esophageal stethoscope. Depth of anesthesia was monitored using a bispectral index (BIS). A gauze pad that had been rolled was placed in the mouth to prevent lingual damage during neurophysiologic monitoring. Two large bore intravenous cannulae and an arterial cannula were placed in all patients. A central venous catheter was placed in 10 patients. To facilitate SSEP and MEP monitoring, total intravenous anesthesia (TIVA) was provided by continuous infusions of propofol, remifentanil and dexmedetomidine. No additional doses of a neuromuscular blocking agent were administered. The dexmedetomidine was started at 0.5 µg/kg/hour without a loading dose. The propofol was started at 100-120 µg/kg/min and titrated to maintain the BIS at 40-60. The remifentanil was started at 0.1 µg/kg/min and increased as needed to maintain controlled hypotension with a mean arterial pressure (MAP) of 50-65 mmHg. The patient was turned prone onto a Jackson table and a prone pillow to prevent pressure to the eyes and face. Once positioned prone, a forced air heating device was used to maintain normothermia. The antifibrinolytic agent, ε-amino caproic acid (EACA), was administered as a bolus dose of 100 mg/kg followed by an infusion of 10 mg/kg/hour until the wound was closed. Isotonic fluids were administered to provide maintenance fluids, correct the deficit, and replace third space losses and blood loss. All patients received 500 ml of a hydroxyethyl starch solution at the start of the procedure. As this was not a prospective study, the fluid therapy was not controlled. One peripheral IV or one port of the central line was used to administer lactated Ringer’s (50-100 mL/hour), remifentanil, propofol, dexmedetomidine, EACA, and clevidipine via infusion pumps. The other IV was used via a free flowing administration set and a fluid warmer to administer replacement fluids, colloids, and blood products as needed.

**CLEVIDIPINE:** If the MAP was ≥65 mmHg despite remifentanil at 0.3 µg/kg/min, clevidipine was added to maintain the MAP at 50-65. Clevidipine was administered using the standard commercially available solution (0.5 mg/mL). The clevidipine infusion was started at 0.5 µg/kg/min in 4 patients and at 1 µg/kg/min in 16 patients. The infusion was increased in increments of 0.5-1 µg/kg/min every 2-3 minutes to achieve the desired MAP. The target MAP was achieved at ≤5 minutes in 15 of the 20 patients and at ≤10 minutes in the other 5 patients. The mean time to achieve the desired MAP was 4.75 ± 2.2 minutes. The maintenance infusion rate of clevidipine varied from 1 to 5 µg/kg/min (2.9 ± 0.7 µg/kg/min). The clevidipine infusion was administered for 120 to 210 minutes (151.3 ± 27.9 minutes). With the administration of clevidipine, HR increased from a baseline of 76 ± 14 to 92 ± 11 beats/minute (p < 0.05). The HR increase was ≥20 beats/minute in 4 patients.
Intermittent doses of metoprolol were used in 3 patients to control the HR increase. In the 14 patients undergoing posterior spinal fusion, the baseline PaO$_2$ decreased from 262 ± 19 mmHg to a low of 184 ± 16 mmHg during the clevidipine infusion (p <0.1). When the clevidipine infusion was discontinued, the next PaO$_2$ value increased to 244 ± 21 mmHg (p = NS when compared to baseline). No excessive hypotension was noted. A triglyceride level was drawn in 6 patients who received clevidipine with propofol and was elevated in 3 patients (≥150 mg/dL, high level 328 mg/dL). When the clevidipine infusion was discontinued, MAP returned to baseline at ≤5 minutes in 16 of the 20 patients and at ≤10 minutes in the other 4 patients. The time for the MAP to return to baseline was 5.3 ± 2.4 minutes.

All patients maintained a urine output ≥ 2 mL/kg/hour during the period of controlled hypotension. The duration of the surgical procedures varied from 235 to 395 minutes (255 ± 38 min). The estimated blood loss varied from 2550 to 1800 mL (740 ± 288). Seven patients received homologous packed red blood cells. No other blood products were administered.

**Discussion**

Clevidipine shares similar structural and hemodynamic effects with nicardipine. Like nicardipine, it is an intravenous dihydropyridine calcium channel antagonist whose primary hemodynamic effect is vasodilatation of the arterial bed.$^{10}$ Metabolism by non-specific blood and tissue esterases results in a half-life of 1-3 minutes. In adult cardiac surgical patients, Levy et al. prospectively compared clevidipine with placebo in adults who presented with preoperative hypertension defined as a systolic blood pressure (sBP) ≥140 mmHg.$^6$ A clevidipine infusion ranging from 0.4 µg/kg/min to a maximum of 8 µg/kg/min reduced sBP by ≥15% in 92.5% of patients compared to only 17.3% of placebo patients. The median time to sBP control was 6 minutes (95% confidence interval: 6 to 8 minutes). A mild increase in HR was noted from 71 beats/minute to a maximum value of 84 beats/minute. There were no differences between clevidipine and placebo in regards to the adverse effect profile.

The ESCAPE-2 trial compared clevidipine (0.4 up to 8 µg/kg/min) with placebo in the treatment of postoperative hypertension (sBP ≥140 mmHg) in adult cardiac surgical patients.$^7$ Systolic BP reduction ≥15% was achieved in 91.8% of the patients receiving clevidipine versus 20.4% with placebo (p <0.0001). The median time to sBP control was 5.3 minutes (95% confidence interval: 4 to 7 minutes).

The potential utility of clevidipine has also been demonstrated in comparison to other antihypertensive agents.$^{11}$ When 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 than with nitroglycerin (p = 0.0006) or SNP (p = 0.003). No difference was noted when compared with nicardipine. Mortality was lower with clevidipine than sodium nitroprusside (p = 0.04).

To date, there are only two previous reports regarding the use of clevidipine in the pediatric-aged patient.$^{8,9}$ The first study outlined the use of clevidipine pre-, intra- and postoperatively in doses ranging from 0.5 to 3.5 µg/kg/min in a cohort of 10 patients, ranging in age from 9 to 18 years.$^8$ The clevidipine infusion was initiated at 0.5 µg/kg/min in 8 patients and at 1 µg/kg/min in the other 2 patients and then titrated up in increments of 0.5 µg/kg/min every 3-5 minutes to achieve effective BP control. The higher end of the dosing range was needed for the induction of controlled hypotension during spinal surgery. Two of the 10 patients required intermittent doses of metoprolol to control an associated increase in HR. No adverse effects such as
excessive hypotension were noted.

The second study reported effective postoperative BP control following cardiac surgery for congenital heart disease in 14 patients who ranged in age from 11 months to 15 years. Clevidipine was administered as either a continuous infusion or a bolus dose. The continuous infusion was used for control of either postoperative BP or intraoperative mean arterial pressure (MAP) during cooling and cardiopulmonary bypass (CPB) while the bolus dose was used for BP control during emergence from anesthesia. The continuous infusion was started at 1 μg/kg/min and increased in increments of 0.5-1 μg/kg/min. For postoperative BP control, dosing requirements varied from 1 to 7 μg/kg/min with the target BP achieved within 5 minutes in all patients. Two patients were treated with either intravenous or oral propranolol for an increase in HR. Effective control of MAP could not be achieved during CPB and cooling (core body temperature 28-32°C) even with doses as high as 10 μg/kg/min. Clevidipine was effective when administered as a bolus dose of 10-15 μg/kg to control BP during emergence from anesthesia.

For the first time, we report experience demonstrating the efficacy of clevidipine in providing CH during spinal surgery. The clevidipine infusion was started at either 0.5 or 1 μg/kg/min and increased in increments of 0.5-1 μg/kg/min every 2-3 minutes as needed. The desired MAP of 50–65 mmHg was achieved in less than 10 minutes in all of the patients at an average time of 4.75 minutes after starting the infusion. Maintenance infusion requirements varied from 1 to 5 μg/kg/min with an average of 2.9 μg/kg/min. When the clevidipine infusion was discontinued, MAP returned to baseline at ≤5 minutes in 16 of the 20 patients and at ≤10 minutes in the other 4 patients. The time for the MAP to return to baseline was 5.3 ± 2.4 minutes.

We found adverse effects to be relatively uncommon in our cohort of patients. No excessive hypotension was noted. However, as a vasodilator, it is not unexpected that reflex tachycardia may occur. This effect tended to be greater than that reported previously with nicardipine and also greater than that reported in adults trials with clevidipine. Although the effect was generally mild, treatment with a β-adrenergic antagonist was deemed necessary in 3 of the 20 patients and there was an average HR increase of 16 beats/minute in our cohort of patients. As a direct acting vasodilator, a second effect that was seen with clevidipine was a decrease in PaO₂ likely related to inhibition of hypoxic pulmonary vasoconstriction. This effect was not of clinical significance in our patient population, but should be considered in patients at risk for hypoxemia due to intrinsic lung disease. As clevidipine is administered in a lipid emulsion in a concentration of 0.5 mg/mL, a TG level was obtained in 6 patients who received clevidipine with propofol. The TG level was mildly elevated in 3 patients with a high value of 328 mg/dL (normal value: 50-150 mg/dL).

In summary, our initial clinical experience demonstrates the efficacy of clevidipine for CH during spinal surgery in adolescents. Given its rapid metabolism by tissue esterases, it can be easily titrated by continuous infusion to maintain the desired MAP with a rapid onset of action. Although its hemodynamic effects are similar to those of nicardipine, should adverse effects occur, its effect dissipate rapidly unlike those of nicardipine. Future studies, with a direct comparison to other commonly used agents, are needed to better define the role of clevidipine for CH and determine its advantages and disadvantages as well as its effects on estimated blood loss.
References