Pheochromocytomas are rare tumors that produce excessive epinephrine and norepinephrine, leading to multiple manifestations of catecholamine surges. Acute intraoperative hypertension during pheochromocytoma resection requires prompt control to avoid major and potentially lethal cardiac and neurologic complications. This article reports the planned and successful use of clevidipine (Cleviprex) as the “sole agent” for intraoperative blood pressure management in 2 adult patients with a diagnosis of pheochromocytoma undergoing elective open adrenalectomy. Clevidipine effectively and promptly provided predictable blood pressure control in both patients.

Keywords: Calcium channel blocker, catecholamine surge, clevidipine, intraoperative hypertension, pheochromocytoma.

Pheochromocytoma is a rare tumor of the chromaffin tissue found in the adrenal glands causing the release of excessive amounts of norepinephrine and epinephrine. The common current practice is to medicate with oral α-blockers preoperatively, followed by β-blockers if needed. Intraoperative control of hypertension is usually achieved with intravenous α-blockers or with sodium nitroprusside. Phentolamine, one of the most commonly studied and used α-blockers in pheochromocytoma management, has intermittently been unavailable in the US market. Current supplies are limited and soon will become nonexistent. Because of the rebranding of sodium nitroprusside, the cost has grown exponentially to nearly 10 times its previous value. The need for an effective, readily available, and affordable drug is apparent.

Clevidipine butyrate (Cleviprex, The Medicines Company, Parsippany, NJ) is a dihydropyridine l-type calcium channel blocker that reduces arterial blood pressure by decreasing systemic vascular resistance. It has been approved for intravenous treatment of essential and perioperative hypertension. Because of rapid metabolism by blood and extravascular ester hydrolysis, clevidipine has a fast onset, brief duration of action, and a short half-life of approximately 1 minute.

Case Summary
Two patients, a 43-year-old man (case 1) and a 37-year-old woman (case 2) with average body habitus, each presented to our hospital with periodic episodes of hypertension, diaphoresis, and palpitations. Both patients did not have any other remarkable medical history. The diagnosis of pheochromocytoma was made based on finding elevated plasma catecholamine levels and their urine metabolite concentrations, along with the presence of hypervascular adrenal masses on the patients’ computed tomographic angiograms.

Each patient was started on an oral regimen of prazosin hydrochloride (α-adrenergic blocker) and scheduled for open adrenalectomy after 3 weeks but did not need preoperative β-blockers. Before surgery neither patient exhibited symptomatic orthostatic hypotension or a marked difference between standing and supine blood pressure.

In the surgical suite holding area, they were normotensive with baseline blood pressures of 115/70 and 140/80 mm Hg, and their heart rates were 75/min (case 1) and 82/min (case 2) in normal sinus rhythm. We planned on using clevidipine as the primary agent to manage intraoperative hypertension, with other antihypertensive agents (nitroprusside sodium, nitroglycerin, magnesium sulfate, and hydralazine) prepared as a backup. After premedication with intravenous midazolam and before each patient entered the operative suite, arterial access was obtained. Propofol (2 mg/kg), remifentanil (1 µg/kg), and vecuronium (0.1 mg/kg) boluses were used for anesthesia induction, and a clevidipine infusion was initiated at a rate of 2 mg/h immediately thereafter. During direct laryngoscopy and intubation, mild blood pressure elevation was noted in both patients. A 1-mg intravenous bolus of clevidipine resulted in prompt control of systolic blood pressure from 170 to 130 mm Hg and from 185 to 140 mm Hg in less than 90 seconds.

Anesthesia was maintained with sevoflurane (1.5%-2%) and a continuous infusion of remifentanil (0.05-1 µg/kg/min) to achieve bispectral index values between
neurologic complications.11-13 lead to major and potentially fatal cardiovascular and epinephrine release surges from these tumors can be charged to home on postoperative day 1. Both patients were successfully extubated in the operating room at the conclusion of their procedures. They remained hemodynamically stable, and both were discharged to home on postoperative day 1.

Discussion

Pheochromocytomas present a perioperative hemodynamic challenge.7 These tumors originate from chromaffin cells and usually exist in the adrenal gland. Catecholamine-secreting masses may be extra-adrenal (sympathetic chain, mediastinum, heart, and urinary bladder) in about 10% of cases and are called paragangliomas. The incidence of pheochromocytomas and paragangliomas is about 1 in 2,000.1,8 The clinical presentation is usually with nonspecific symptoms such as headache, sweating, and palpitations.9,10 Norepinephrine and epinephrine release surges from these tumors can lead to major and potentially fatal cardiovascular and neurologic complications.11-13

Although there is no consensus regarding the preferred medications for preoperative blood pressure control in patients with pheochromocytoma, phenoxybenzamine (a noncompetitive, nonselective α-adrenergic blocking agent) is usually prescribed for 2 weeks to allow for spontaneous intravascular volume expansion. Subsequently, careful initiation and titration of β-adrenergic blockers may be needed to treat any associated tachycardias after adequate α-blockade. The Table lists medications that have been used for the management of intraoperative hypertensive crisis, including sodium nitroprusside, nicardipine, clevidipine, labetalol, esmolol, nitroglycerin, phenolamine, hydralazine, magnesium sulfate, and fenoldopam.3,4,14,15 Because of various manufacturing and regulatory factors affecting the pharmaceutical industry, drug shortages continue to rise dramatically. Many of these drugs have been intermittently unavailable or are no longer available because of suspended production.17 Health care professionals are increasingly concerned about the effects that shortages have on their patients with acute or emergent conditions. This leads to a dire need for therapeutically equivalent alternatives that are safe and preferably have comparable costs. Pheochromocytoma and acute hypertensive crisis are prime examples.

Clevidipine butyrate (Cleviprex; The Medicines Company, Parsippany, NJ) is an intravenous ultrashort-acting, third-generation dihydropyridine calcium channel blocker that causes selective arterial vasodilation. This leads to a predictable dose-dependent decrease in afterload and peripheral vascular resistance. Because of its rapid metabolism by plasma esterases, the initial half-life of clevidipine is about 1 minute and the terminal half-life is 15 minutes with minimal accumulation.18 Clevidipine is one of the few intravenous solutions that is prepared in a lipid emulsion. Previously, because of infection risks, once the stopper on the vial was punctured, the medication had a 4-hour limit until it is was required to be discarded. Recent preparations of the solution contain EDTA (similar to propofol), allowing single-bottle infusions of up to 12 hours in duration.6 This has greatly reduced the cost of continuous infusions. However, it should be noted that strict aseptic technique is imperative. Clevidipine is contraindicated in patients who have impaired lipid metabolism, soy or egg allergies, or severe aortic stenosis.5

Clevidipine was approved in 2008 for the management of acute hypertension in various clinical scenarios.19-22 Results of clinical trials showed that clevidipine was more effective in blood pressure control than nitroglycerin (P < .0006) and sodium nitroprusside (P < .003) are and required fewer interventions than nicardipine did to maintain the blood pressure within a narrower predetermined range.23,24 The tight hemodynamic control of clevidipine can lead to decreased perioperative complications and increased survival.25 Although clevidipine has not been formally studied for blood pressure control in the setting of pheochromocytoma, its ideal pharmacologic antihypertensive characteristics make it an attractive option for hypertensive crisis management in these cases.6,26 Clevidipine has a fast onset and short duration of clinical effects because of rapid elimination that is independent of hepatic and renal clearance, thus providing easy titration with precise hemodynamic control.27

Despite these facts, it seems that clevidipine remains underused in the perioperative management of pheochromocytomas and paragangliomas. One author reported
<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Dosage</th>
<th>Onset</th>
<th>Duration</th>
<th>Comments</th>
<th>Wholesale Acquisition Cost (US $)</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium nitroprusside</td>
<td>Arteriolar and venous dilator</td>
<td>0.25-10 µg/kg/min</td>
<td>Seconds</td>
<td>3 min</td>
<td>Cyanide toxicity with prolonged or too rapid infusion</td>
<td>50 mg/2 mL</td>
<td>606.53</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Calcium channel blocker</td>
<td>5 mg/h increased by 2.5 mg/h every 5 min up to 30 mg/h</td>
<td>5-15 min</td>
<td>3-6 h</td>
<td>Reflex tachycardia</td>
<td>2.5 mg/mL—10 mL; 40 mg/200 mL</td>
<td>18.96; 178.81</td>
</tr>
<tr>
<td>Clevidipine</td>
<td>Calcium channel blocker</td>
<td>1-2 mg/h, doubling dose at 90-sec intervals, up to max 16 mg/h</td>
<td>2-4 min</td>
<td>5-15 min</td>
<td>Reflex tachycardia</td>
<td>0.5 mg/mL—50 mL; 0.5 mg/mL—100 mL</td>
<td>65.00; 130.00</td>
</tr>
<tr>
<td>Labetalol</td>
<td>β- and α-adrenergic blocker</td>
<td>20 mg initially, then 20-80 mg every 10 min or 2 mg/min (300 mg max)</td>
<td>5-10 min</td>
<td>3-6 h</td>
<td>Not for patients with bronchospasm, cardiogenic shock, heart block, or severe bradycardia</td>
<td>5 mg/mL—4-mL syringe; 5 mg/mL—20 mL; 5 mg/mL—40 mL</td>
<td>4.76; 2.16; 4.32</td>
</tr>
<tr>
<td>Esmolol</td>
<td>β-blocker</td>
<td>0.5-1 mg/kg over 1 min, then 50-300 µg/kg/min</td>
<td>1 min</td>
<td>10-20 min</td>
<td>For patients with aortic dissection or postoperative hypertension</td>
<td>10 mg/mL—10 mL; 10 mg/mL—250 mL; 20 mg/mL—250 mL</td>
<td>6.12; 184.39; 198.68</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Venous and arteriolar dilator</td>
<td>5-100 µg/min</td>
<td>2-5 min</td>
<td>5-10 min</td>
<td>For patients with cardiac ischemia or postoperative hypertension</td>
<td>5 mg/mL—10 mL; 50 mg/250-mL bottle</td>
<td>10.00; 7.17</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Nonselective α-blocker</td>
<td>5-15 mg</td>
<td>1-2 min</td>
<td>3-10 min</td>
<td>For patients with pheochromocytoma, cocaine intoxication, and MAO interactions</td>
<td>5 mg/2 mL</td>
<td>141.17</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Arteriolar dilator</td>
<td>5-10 mg every 20-30 min</td>
<td>10-30 min</td>
<td>2-4 h</td>
<td>May precipitate angina, myocardial infarction; not used for aortic dissection</td>
<td>20 mg/mL</td>
<td>11.28</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>Inhibits catecholamine release and receptors</td>
<td>4-g loading dose over 20 min, then 2 g/h infusion</td>
<td>15-30 min</td>
<td>3-6 h</td>
<td>May increase the duration of a neuromuscular blockade</td>
<td>1 g/2 mL; 1 g/100 mL; 2 g/50 mL</td>
<td>1.29; 6.16; 10.62</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>Dopamine (DA1) agonist - arteriolar dilator</td>
<td>0.1 µg/kg/min initially, then 0.03-0.3 µg/kg/min</td>
<td>5 min</td>
<td>10 min</td>
<td>For patients with impaired renal function</td>
<td>10 mg/mL</td>
<td>326.89</td>
</tr>
</tbody>
</table>

Table. Commonly Used Intravenous Medications for the Management of Hypertensive Crisis

aCost values from McKesson Corp, 2015.16
bAvailability data from American Society of Health-System Pharmacists, 2015.17

(Adapted from and modified with permission from The Medical Letter.15)
the successful utilization of clevidipine to manage severe and unexpected intraoperative hypertension caused by an undiagnosed pheochromocytoma after failed control by administering a variety of other medications. Only one other published report described the planned use of clevidipine in the elective resection of a catecholamine-secreting paraganglioma, in a pediatric patient. To our knowledge, based on a literature search performed on June 2, 2015, there were no published reports for the planned use of clevidipine in the elective resection of pheochromocytoma or paraganglioma tumor (known diagnosis) in the adult population.

In addition to administering clevidipine as an intravenous infusion in our patients, we used clevidipine boluses for the management of intraoperative hypertensive crisis. This decision was based on reviewing the preliminary results from a recent study (SPRINT) designed to evaluate the pharmacodynamics, as well as the efficacy and safety, of the administration of 3 different bolus doses of clevidipine (125, 250, and 500 µg) for the management of blood pressure in cardiac surgical patients. With clevidipine bolus injection, the blood pressure reduction was generally rapid and the recovery to baseline was fairly uniform. The maximum change in blood pressure from baseline after a bolus dose of 500 µg was −22% (± 9%). The times until 5%, 10%, and 15% blood pressure reduction were 0.8, 1.1, and 1.2 minutes, respectively, with the onset of maximum reduction occurring around 2 minutes after the bolus injection. Time to recovery for bolus dosing was approximately 50% faster than with a clevidipine infusion. The times to 50% and 90% blood pressure recovery after the administration were 2.9 and 6.8 minutes, respectively. The SPRINT study results showed that rapid clevidipine administration as a small intravenous bolus can be safely administered to acutely decrease the systemic blood pressure. None of the patients experienced unintentional hypotension (systolic blood pressure ≤ 85 mm Hg), and the change in heart rate was 3.1/min (± 2.73/min).

During our intraoperative hemodynamic management of both patients, we used esmolol boluses for heart rate control. In patients with a hyperadrenergic state, β-blockade alone is generally avoided to prevent unopposed α-adrenergic stimulation, which can lead to coronary vasoconstriction and further increases in hypertension. After ensuring adequate depth of anesthesia and analgesia and after vasodilation had been achieved with a short-acting direct vasodilator (as evidenced by a decrease in blood pressure), esmolol was given to lower the heart rate. Several case reports have shown that esmolol may be the better choice in perioperative management of sympathetic surge because of its short duration of action.

Based on our clinical experience, we suggest that clevidipine can be considered a viable and effective alternative for use in patients with pheochromocytoma to the other commonly used agents in practice (eg, intravenous α-blockers and nitroprusside sodium) during the perioperative period. Further prospective research studies are required to clarify the efficacy, safety, and limitations of clevidipine for perioperative hemodynamic management in adult and pediatric patients with catecholamine-secreting tumors.

REFERENCES

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DISCLOSURES
The authors have declared they have no financial relationships with any commercial interest related to the content of this activity. The authors did discuss off-label use within the article.

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