Use of Clevidipine for Intraoperative Hypertension Caused by an Undiagnosed Pheochromocytoma: A Case Report

Jonathan P. Kline, CRNA, MSNA

The acute intraoperative hypertension and tachycardia caused by an undiagnosed pheochromocytoma is a rare event for the anesthesia provider. If treatment is not prompt and successful, permanent and possibly lethal complications can ensue. This article reports what the author believes to be the first case study in which clevidipine (Cleviprex) was successfully used to treat a suspected, and later diagnosed, pheochromocytoma.

Keywords: Catecholamine response, clevidipine (Cleviprex), intraoperative hypertension, pheochromocytoma.

Pheochromocytoma is a rare tumor, usually in the adrenal gland, that produces excessive catecholamines such as epinephrine and norepinephrine. The catecholamine release usually occurs as a response to stress, such as the induction of anesthesia, or tumor manipulation. Western countries have an incidence of about 1:6,500 or about 500 to 1,000 cases per year. Treatment is targeted toward α- and β-adrenergic antagonism. In previously diagnosed cases, the treatment regimen included both α- and β-blockers for at least several days before tumor resection.

A good deal of current literature outlines diagnoses, treatment, and intraoperative strategies for handling the invariable catecholamine surges. This article reports what we believe is the first time that clevidipine has been used for this purpose. The basics of pheochromocytomas and clevidipine are discussed, as well as the intraoperative course of this particular event.

Pheochromocytoma

According to an article in the New England Journal of Medicine, the first description of a catecholamine-secreting tumor was made in 1886, by Felix Frankel. Dr Ludwig Pick first coined the term pheochromocytoma in 1912. A pathologist, he noted the tumor’s colorful changes when contacted with fixatives. The first documented resection of a pheochromocytoma occurred in Europe in 1926. Dr Rouks completed the first American removal of such a tumor at the Mayo Clinic in 1927. The early days of pheochromocytoma resection presented mortality rates greater than 50% due to the exaggerated cardiovascular events that occurred intraoperatively. Modern practices boast mortality rates close to zero. This is due, in part, to the advent of new medications used before, during, and after anesthesia.

Pheochromocytoma has a varied presentation. Common signs and symptoms include headaches, intermittent sweating, flushing, dizziness, and palpitation episodes. Less common signs and symptoms include abdominal or flank pain, abdominal pulsations, chest pain, and pulmonary edema. These clinical presentations can confuse providers in the setting of surgical or traumatic pain, fever, or pregnancy. Because these episodes are usually self-limiting, the diagnosis can be elusive. Traditional diagnostic markers include urine vanillylmandelic acid levels (the principal end product of epinephrine and norepinephrine hepatic metabolism), urine metanephrine levels, serum catecholamine levels, and computed tomographic (CT) scan.

Once the diagnosis of pheochromocytoma has been made, treatment is focused on stabilization of catecholamine surges before tumor resection. This generally includes α- and β-adrenergic blocking agents. Postoperatively, catecholamine withdrawal can induce hypotension, requiring vasopressor support.

Intraoperative care is considerably more complex. The hypertension and tachycardia can be resistant to many of the traditional modalities, particularly if the diagnosis has not been established. It has long been thought that tumor manipulation causes the greatest cardiovascular derangements. However, recent literature supports the idea that the induction of general anesthesia, rather than tumor resection, induces the larger catecholamine surge.

Nearly all patients with pheochromocytomas will present to surgery with proper management and can be well controlled with the various traditional regimens. The Table summarizes many of the well-known intravenous medicines in the anesthesia arsenal for this purpose. It also includes 2 new medicines, landiolol and clevidipine. Landiolol is a relatively new, ultrashort-acting, β-adrenergic blocking agent. Clevidipine is a new ultrashort-acting, selective calcium channel blocker.
A patient presented for maxillofacial surgery after an assault in a prison. He sustained a right orbital rim fracture, right maxillary fracture, and right displaced mandible fracture. The surgical plan included repair of all facial fractures during the upcoming general anesthetic. Gross swelling was noted around the entire right side of his face, but there was no airway involvement. Preoperative assessment included weight of 105 kg, an ASA physical status of 2, and a Mallampati grade 3 airway. Airway assessment was difficult secondary to the patient’s decreased ability to open his jaw because of pain. He denied any medical history. His past surgical history included only a tonsillectomy as a child, with no reported anesthesia complications. He was otherwise in good health with the exception of a few facial fractures.

General anesthesia was commenced without incident except for a lingering low-grade hypertension and tachycardia (heart rate 105/min and blood pressure around 150/90 mm Hg). The surgeon injected lidocaine 2% with epinephrine, first at the orbital rim, with a single Carpu syringe, around 3 mL. During the case, a total of 10 mL of lidocaine with epinephrine was injected. There was no evidence of intravascular injection noted following each infiltration. The case proceeded for several hours with nothing noteworthy other than an outlying need for narcotics despite local infiltration by the surgeon. This was attributed to increased anesthesia requirements due to his large muscular size, and a long-term intake of illicit drugs was suspected.

After a change in anesthesia providers, it was noted that the patient was requiring 2.5 minimal alveolar concentration of sevoflurane and in excess of 20 mL of fentanyl (about 6 μg/kg per hour). Despite an additional 10 mL of fentanyl, the patient’s blood pressure began to precipitously rise to 200/110 mm Hg. The patient received 3 escalating doses of esmolol, 0.5 mg/kg, 1 mg/kg, and 2 mg/kg. The blood pressure continued to rise to 220/112 mm Hg, and the heart rate was approximately 130/min. Labetalol, 20 mg, was then given, and shortly after no effect was noted. The blood pressure rose to 250/120 mm Hg, and the heart rate was in the range of 140/min. Hydralazine, 20 mg, was then given without a single decrease in hemodynamics. The surgeon was asked to re-inject local anesthetic to rule out an acute pain response and to hasten the case, while help was called. The surgeon quickly closed the case while the anesthesiologist arrived, and an arterial line was placed. The patient received nitroglycerine boluses of 20, 30, 50, and 100 μg. By this time, the blood pressure was 290/150 mm Hg and the heart rate was in excess of 160/min.

Upon completing the case, the surgeon rechecked the chart and noted that a small lesion was reported on the kidney as an incidental finding. This information, in combination with this unusual and terrifying hyperdynamic state, put an undiagnosed pheochromocytoma at the top of our differential diagnoses. The pharmacy was notified of the emergency and sent a quantity of phentolamine. Boluses of 5 mg finally relieved the hypertension, but only for a brief time. A quick calculation revealed that we could control this malignant hypertension with phentolamine for only about 2 hours, and then a secondary plan would need to be instituted.

The ECLIPSE trials of 2007 and 2008 demonstrated that clevidipine was an excellent alternative to nitroglycerine during cardiac surgical intervention and was therefore selected for its reliable relief of hypertension. The patient was then placed on a clevidipine drip with immediate cessation of the hypertension. An initial dose of 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
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<tbody>
<tr>
<td>Hydralazine (Apresoline)</td>
<td>α-blocker</td>
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<tr>
<td>Phentolamine (Regitine)</td>
<td>α -blocker</td>
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<tr>
<td>Clevidipine (Cleviprex)</td>
<td>Calcium channel blocker</td>
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<tr>
<td>Nicardipine (Cardene)</td>
<td>Calcium channel blocker</td>
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<tr>
<td>Esmolol (Brevibloc)</td>
<td>β-blocker</td>
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<tr>
<td>Labetalol (Trandate)</td>
<td>β-blocker</td>
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<tr>
<td>Landiolol</td>
<td>β-blocker</td>
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<tr>
<td>Metoprolol (Lopressor, Toprol-XL)</td>
<td>β-blocker</td>
</tr>
<tr>
<td>Nitroglycerine (Nitro-Bid, Tridil)</td>
<td>Nitrates</td>
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<tr>
<td>Sodium nitroprusside (Nipride)</td>
<td>Nitrates</td>
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Table. Intraoperative Intravenous Antihypertensive Agents
mg/min was quickly followed by escalating doses every 2 minutes until a dose of 5 mg/min was achieved. This allowed the patient to be extubated in the operating room and safely transported to the postanesthesia care unit.

The following day urine catecholamine levels confirmed the diagnosis of pheochromocytoma. We later learned that the patient had been complaining of headaches and dizziness but attributed it to stress. The patient underwent stabilization of hypertension over the next several days. He subsequently underwent a laparoscopic resection of the tumor and had a full recovery.

**Conclusion**
The severe intraoperative hypertension caused by an undiagnosed pheochromocytoma is a rare and challenging event for the anesthesia provider. There are a variety of medications for the treatment of acute hypertension. However, the extreme nature of pheochromocytoma-induced hypertension may be resistant to traditional modalities. Clevidipine was used successfully for the first time to ameliorate this life-threatening event. This case illustrates the difficulty in prompting this diagnosis. This difficulty may be the result of false conclusions based on the patient's recent place of origin and the rarity of such a diagnosis. As it happened, the patient was a prison guard assaulted in the line of duty.

**REFERENCES**

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