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Esmolol Use during Resection of Pheochromocytoma: Report of Three Cases

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Intraoperative care of patients with pheochromocytoma presents many difficult anesthetic management problems. Several anesthetic techniques and pharmacologic therapies have been advocated for use intraoperatively, including total epidural blockade,[1] isoflurane general anesthesia,[2] vecuronium for muscle relaxation,[3,4] or other general inhalation or intravenous agents.[5] Preoperative alpha-adrenergic blockade is one of the major factors reducing perioperative morbidity of patients with pheochromocytoma.[5] Beta-adrenergic blockade is commonly used to control tachycardia or arrhythmias after alpha-adrenergic blockade has been established. Esmolol, a titrable, ultra-short acting β-adrenergic blocking drug[6] has hemodynamic effects that may be uniquely suited for the intraoperative management of pheochromocytoma. In the literature, esmolol use in the intraoperative management of pheochromocytoma has been suggested,[7] and recently reported in one patient.[8] We report our experience using esmolol in three patients undergoing adrenalectomy for removal of pheochromocytoma.

CASE REPORTS

Case 1. A 39-yr-old, 80-kg man presented with right temporoparietal headache; ophthalmoplegia of cranial nerves III, IV, and VI; palpitations, nausea, and hyperglycemia. A right carotid-cavernous sinus fistula was detected on angiography. Because of complaints of leg pain and absence of pedal pulses on physical examination, an aortic angiogram was obtained that demonstrated a right supraadrenal mass and bilateral occlusion of the external iliac arteries. During angiogram, blood pressure increased to 230/120 mmHg, pulse increased to 140/min, and chest pain occurred. Acute pulmonary edema was noted on physical exam and chest x-ray. Plasma epinephrine was 9948 pg/ml (normal < 90 pg/ml). Plasma norepinephrine was 16000 pg/ml (normal < 600 pg/ml). The urinary metanephrines of 38 mg/24 h (normal 0.3–0.9 mg/24 h) and vanillyl-mandelic acid (VMA) of 88 mg/24 h (normal 2.2–10 mg/24 h) confirmed the presence of pheochromocytoma.

The patient received phenoxybenzamine 30 mg PO BID and metoprolol 25 mg PO Q8H for 1 week. Blood pressure was stable at 120–150/70–90 mmHg. Hematocrit decreased from 53% to 34%. Six hours preoperatively, an arterial catheter and oximetric pulmonary artery catheter were inserted, displaying central venous pressure (CVP) −5 mmHg, pulmonary artery pressure (PAP) 13/3 mmHg, pulmonary capillary wedge pressure (PCWP) 0 mmHg, and cardiac output (CO) 5.2 l/min. Catheter position and pressure measurements were confirmed by chest x-ray, pressure wave-forms, and recalibration of transducers. One liter of 5% albumin and 1 unit of PRBC increased the CVP to −1 mmHg, PAP to 19/10 mmHg, PCWP to 10 mmHg, and CO to 5.9 l/min. The patient then received midazolam 5 mg IM as preanesthetic medication and was brought to the operating room.

Immediately before induction, blood pressure was 140/80 mmHg, pulse 110/min, CVP −3 mmHg, PA 10/4 mmHg, PCWP 0 mmHg, and CO 6.0 l/min, with mixed venous saturation 76%. A lumbar epidural catheter was inserted in the L2–L3 interspace and 20 ml of bupivacaine 0.5% administered to produce a T4 sensory level. General anesthesia was then induced with thiopental 350 mg, alfentanil 2500 μg, and lidocaine 100 mg, with vecuronium 10 mg for muscle relaxation. Anesthesia was maintained with bupivacaine 0.5%, air/oxygen, and isoflurane 0.4–1.5%, while muscle relaxation was maintained with vecuronium 10 mg. Nitroprusside 200 μg/ml and esmolol 10 mg/ml infusions were maintained to keep systolic blood pressure between 120–160 mmHg and pulse 90–110. Nitroprusside was initiated at a rate of 1 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1} and the dose was adjusted based on intra-arterial blood pressure. The patient received a loading dose of esmolol 500 $\mu g \cdot kg^{-1}$ over 1 min followed by an infusion of 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 min until the blood pressure and pulse started to decrease. The infusion was maintained at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until blood pressure and pulse stabilized. The infusion was decreased or discontinued when appropriate, based on measurement of heart rate. Tumor manipulation was associated with episodes of hypertension 190–210/100–120 mmHg and pulse 130. These were easily and immediately treated by increasing the infusion rates of nitroprusside and esmolol. As the adrenal vein was tied, nitroprusside and esmolol were discontinued. Two minutes later, blood pressure rose to 230/120 mmHg and the pulse increased to 140. Another vein draining the adrenal was located and ligated. After ligation and tumor removal, blood pressure decreased to 80/50 mmHg with pulse 90/min. One liter of 6% hetastarch increased blood pressure to 100/60 mmHg. The total nitroprusside dose was 30 mg/2.5 h (mean 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and the total esmolol dose was 2.5 gm/2.5 h (mean 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Epidural morphine 5 mg was administered for postoperative analgesia. The pheochromocytoma was confirmed histologically. The patient recovered with spontaneous resolution of his iliac artery thrombosis and carotid-cavernous sinus fistula.

Case 2. A 56-yr-old, 64-kg man had a 1.5-yr history of hypertension, tachycardia, episodes of diaphoresis, anxiety, and headaches. Urinary metanephrines were 7.3 mg/24 h and VMA 19.2 mg/24 h. Computerized axial tomography revealed a left adrenal mass consistent with pheochromocytoma. The patient received phenoxybenzamine 20 mg PO BID for 6 weeks, and propranolol 5 mg PO QID and Digoxin 0.125 mg PO BID for 1 week. Blood pressure was stable at 110–150/70–80 mmHg. The patient received midazolam 5 mg and meperidine

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50 mg im as preanesthetic medication. In the operating room, 14-gauge intravenous, radial arterial, and pulmonary artery catheters were inserted. Prior to induction, hemodynamic values were BP 120/75 mmHg, CVP 5 mmHg, PAP 22/12 mmHg, and CO 4.6 l/min. General anesthesia was induced with thiopental 200 mg and sufentanil 40 μg, with vecuronium 10 mg for muscle relaxation. Anesthesia was maintained with N_2O/O_2, sufentanil 60 μg, and vecuronium 6 mg. Nitroglycerin 200 μg/ml infusion 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was started to permit volume loading with 5% albumin 500 ml, 6% hetastarch 1000 ml, and lactated Ringers 1000 ml. Nitroprusside 200 μg/ml infusion was started to maintain systolic blood pressure 120–160 mmHg and esmolol 10 mg/ml infusion started to keep pulse 60–80/min. Nitroprusside was initiated at a rate of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and titrated based upon intraarterial blood pressure. The patient received a loading dose of esmolol 500 $\mu g \cdot kg^{-1}$ over 1 min followed by an infusion of 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 min until the blood pressure and pulse started to decrease. The infusion was maintained at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until blood pressure and pulse stabilized. The infusion was decreased or discontinued when appropriate, based on measurement of heart rate. Tumor manipulation resulted in episodes of hypertension 190/100 mmHg and pulse 80, which were easily treated with increased infusion of nitroprusside and esmolol. Hemodynamic parameters were maintained at PAP 22–25/12–15 mmHg and CO 4.6–5.2 l/min by titrating infusions of esmolol and nitroprusside. At the time of tumor venous ligation, blood pressure decreased to 120/70 mmHg and the infusions of nitroprusside, nitroglycerin, and esmolol were discontinued. The pheochromocytoma was confirmed histologically. The mean infusion rates for the operation are esmolol 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$, nitroprusside 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and nitroglycerin 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Case 3. A 52-yr-old, 50-kg woman presented with 8 months of headache, diaphoresis, dizziness, and hypertension. Abdominal CAT scan demonstrated a left adrenal mass. Urinary metanephrines and VMA confirmed the presence of a pheochromocytoma. The patient was treated with phenoxybenzamine 10 mg PO TID and propranolol 20 mg PO TID for 4 months. In the operating room, 14-gauge intravenous, radial arterial, and pulmonary artery catheters were inserted. Initial hemodynamic values were BP 170/90 mmHg, CVP 10 mmHg, PAP 26/14 mmHg, and CO 2.9 l/min. General anesthesia was induced with thiopental 2 $\mu g \cdot kg^{-1}$ and sufentanil 1 $\mu g \cdot kg^{-1}$ with vecuronium 0.12 $mg \cdot kg^{-1}$ for muscle relaxation. Anesthesia was maintained with N_2O/O_2, sufentanil 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$, isoflurane 0–0.8% as needed, and vecuronium 0.04 $mg \cdot kg^{-1} \cdot h^{-1}$. Nitroglycerin 200 μg/ml infusion 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was started to permit volume loading with lactated Ringers 1000 ml, 6% hetastarch 1000 ml, 5% albumin 750 ml, and PRBC 1 unit. Nitroprusside 200 μg/ml infusion was started to maintain the systolic blood pressure 120–160 mmHg and esmolol 10 mg/ml infusion started to keep pulse 70–90/min. Nitroprusside was initiated at a rate of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and titrated based upon intraarterial blood pressure. The patient received a loading dose of esmolol 500 $\mu g \cdot kg^{-1}$ over 1 min followed by an infusion of 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 min until the blood pressure and pulse started to decrease. The infusion was maintained at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until blood pressure and pulse stabilized. The infusion was decreased or discontinued when appropriate, based on measurement of heart rate. Tumor manipulation was associated with an increase of blood pressure to 250/140 and pulse to 100. This was treated effectively with increased infusions of nitroprusside and esmolol. Hemodynamic parameters were maintained at PAP 22–28/10–15 and CO 5–5.6 l/min by titrating the infusions of esmolol and nitroprusside. As the adrenal vein was ligated, the infusions of esmolol, nitroglycerin, and nitroprusside were discontinued. One minute later, blood pressure increased to 230/120 mmHg and pulse 120/min. Another vein draining the adrenal was located and ligated. Blood pressure stabilized at 120/60 mmHg with pulse 70/min. The histologic findings confirmed the diagnosis of pheochromocytoma. During the operation, the average infusion rates were esmolol 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$, nitroprusside 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and nitroglycerin 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Discussion

No anesthetic technique has gained universal acceptance for pheochromocytomas, although many techniques have been advocated, including total epidural blockade,[1] isoflurane,[2] and vecuronium for muscle relaxation.[3,4] No difference in patient outcome between enflurane, halothane, droperidol, and fentanyl (Innovar), or combined regional and light general anesthesia has been noted.[5] After the safe and judicious administration of anesthesia, control of the hemodynamic alterations produced by epinephrine and/or norepinephrine secreting tumors is of primary importance.

Esmolol is uniquely suited for finely controlled titration of β-adrenergic receptor blockade,[6] which may be required during pheochromocytoma resection. Esmolol is metabolized by the red cell cytosol esterase to methanol and an acid derivative.[6] Distribution half-life is 2 min and the elimination half-life is 9 min.[9,10] Esmolol does not interfere with plasma pseudocholinesterase.[11] The recommended loading dose of esmolol is 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 min and 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 4 min, with a maintenance infusion rate of 25–300 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[9] Our patients received a higher second stage infusion in order to more rapidly obtain control of the heart rate. The β_1 selectivity[10,12] of esmolol may allow β_2 stimulated vasodilation by epinephrine secreting tumors.

Nitroprusside infusion provides titrable, immediately acting direct vasodilatation, which allows fine control of blood pressure during hypertensive episodes, including those occurring during pheochromocytoma resection.[13,14] However, arterial vasodilatation may be accompanied by reflex tachycardia. Esmolol infusion provides titrable, short onset, short duration β-blockade which allows fine control of heart rate during episodes of catecholamine excess or reflex tachycardia. Beta-blockade may also be protective against catecholamine-induced cardiomyopathy and ischemia. Together, these drugs provide immediate, titrable therapy for epinephrine and/or norepinephrine release during pheochromocytoma removal.

Nitroglycerin infusion has been advocated for blood pressure control in pheochromocytomas.[15] Preoperative volume loading has also been recommended.[16] Two of our three patients received nitroglycerin infusion 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to permit venodilation and volume loading. Nitroglycerin infusion for volume loading may prevent hypotension after pheochromocytoma removal and infusion discontinuation. The other patient received epidural anesthesia, which also venodilates, permitting volume loading.

These case reports demonstrate how esmolol and nitroprusside were used to control the intraoperative hemodynamic alterations that developed during the resection of a pheochromocytoma. Use of an inhalational general anesthetic may result in a lower intraoperative baseline pressure than occurred in our second and third

patients, who received a predominantly nitrous-narcotic anesthetic. However, regardless of the type of anesthesia received, the rapid alterations in blood pressure and heart rate produced by tumor manipulation would require titratable control of the hemodynamic changes. While the use of nitroprusside infusion during pheochromocytoma resection has been previously described,[13,14,17] the use of esmolol infusion for pheochromocytoma has only recently been described in one patient.[8] In contrast to the report of Nicholas, who used a constant infusion of esmolol 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$, we feel that a varying infusion better utilizes the advantageous pharmacologic properties of this agent to treat sudden alterations in hemodynamics. Titrating the infusion of esmolol to maintain a heart rate of 90–110/min in one patient and 70–90/min in two patients resulted in average infusion rates of esmolol 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$, within the usual range for β-blockade, and higher than the esmolol infusion rate reported by Nicholas.[8] Patients may require different infusion rates of esmolol, depending on the amount of catecholamines released. The short elimination half-lives of esmolol, nitroprusside, and nitroglycerin allowed diagnosis of an additional venous supply or tumor site after ligation of the adrenal vein in two of the three cases presented here.

In summary, the infusions of esmolol and nitroprusside are easily titrated to the varying release of epinephrine and/or norepinephrine during resection of a pheochromocytoma. Esmolol and nitroprusside are ideally suited to aid in the anesthetic management of pheochromocytomas.

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