Use of Dexmedetomidine in a Parturient With Multiple Endocrine Neoplasia Type 2A Undergoing Adrenalectomy and Thyroidectomy: A Case Report

Amanda L. Faulkner, MD, * Eric Swanson, MD, * Thomas L. McLarney, MD, * Cortney Y. Lee, MD, † and Annette Rebel, MD *

Dexmedetomidine is a selective α2-agonist, frequently used in perioperative medicine as anesthesia adjunct. The medication carries a Food and Drug Administration pregnancy category C designation and is therefore rarely used for parturients undergoing nonobstetric surgery. We are reporting the use of dexmedetomidine in the anesthetic management of a parturient undergoing minimally invasive unilateral adrenalectomy for pheochromocytoma during the second trimester of pregnancy. Additionally, because of the multiple endocrine neoplasia type 2A constellation with diagnosis of medullary thyroid cancer, the patient underwent a total thyroidectomy 1 week after the adrenalectomy. (A&A Practice. XXX;XXX:00–00.)

CASE REPORT
A 34-year-old gravida 3 para 2 woman (body weight, 61 kg; body height, 167 cm) at 18 weeks’ gestation presented to her obstetrician and was found to have a single coin-sized neck mass on physical examination. Medullary thyroid carcinoma was diagnosed by fine needle aspiration. Investigational thyroid studies revealed a low-normal thyroid-stimulating hormone level, an elevated calcitonin level, and an elevated carcinoembryonic antigen value (Table). Further laboratory evaluation revealed significantly elevated fractionated metanephrines, confirming the diagnosis of pheochromocytoma. The patient denied palpitations, sweating, or headaches. A magnetic resonance imaging of the abdomen demonstrated a 3-cm left adrenal mass concerning for pheochromocytoma (Figure 1) and a contralateral 1 cm adrenal nodule. On these diagnoses of thyroid carcinoma and pheochromocytoma, the patient admitted to a family history of MEN2A. Her sister was diagnosed with a gene mutation that is associated with MEN2A and MEN type 2B and had a history of metastatic medullary thyroid carcinoma and underwent bilateral adrenalectomies for pheochromocytoma. Her mother was diagnosed with medullary thyroid carcinoma on autopsy. Interestingly, our patient refused genetic testing approximately 3 years before her presentation (at the time of her sister’s diagnosis).

Preoperative Management
Although the patient did not report significant symptoms related to the pheochromocytoma, the patient care team (endocrinologist, oncologist, and surgeon) felt that the pheochromocytoma should be resected before the thyroid mass, and the thyroid malignancy be addressed as soon as possible (before delivery). The aim was to complete all procedures within the second trimester. An organized care plan was created by obstetric, surgical, and anesthesia providers; the plan detailed a minimally invasive adrenalectomy at 22 weeks gestational age, followed by a total thyroidectomy approximately 1 week later. Therefore, the workup and time for hemodynamic optimization were significantly limited. A transthoracic echocardiogram was performed and demonstrated normal cardiac anatomy and unremarkable

From the Departments of *Anesthesiology and †Surgery, University of Kentucky, Lexington, Kentucky.
Accepted for publication July 3, 2018.
Funding: None.
The authors declare no conflicts of interest.
Address correspondence to Annette Rebel, MD, Department of Anesthesiology, University of Kentucky, 800 Rose St, N 202 Lexington, KY 40536. Address e-mail to arebe2@uky.edu.
Copyright © 2018 International Anesthesia Research Society
DOI: 10.1213/XAA.0000000000000861
cardiac function. The baseline blood pressure in the obstetrician office was 140/98, and heart rate (HR) 96 beats per minute (bpm). Alpha blockade was initiated 2 weeks before the adrenalectomy using phenoxybenzamine. Blood pressure measurements fluctuated in the range of 121/80 to 108/67, and HR range 108–90 bpm without endorsement of orthostasis. Further symptomatic management and control of hypertension thereafter were achieved with labetalol. The patient endorsed some dizziness and signs of orthostasis with continued tachycardia at phenoxybenzamine 20 mg orally 3 times daily and labetalol 100 mg orally once daily. At the final clinic appointment before surgery, blood pressure was 112/75, and HR was 94 bpm.

Given the small contralateral adrenal nodule, there was some discussion regarding the need for bilateral adrenalectomy. In a typical setting, functional nuclear imaging is used to help delineate a functional pheochromocytoma from a nonfunctional adenoma. However, in the setting of pregnancy, this option was not ideal. It was felt that the risk to the patient and pregnancy related to resulting adrenal insufficiency with steroid replacement outweighed the potential benefit in removing a potential pheochromocytoma that was likely too small to contribute to the hemodynamic situation. Therefore, only the large adrenal nodule was addressed at this stage to avoid the hormone replacement requirements warranted by a bilateral adrenalectomy during the pregnancy. The patient remained on phenoxybenzamine (lower doses) through the second thyroid surgery as a precaution. It was successfully discontinued after the thyroid surgery.

**Table. Preoperative Laboratory Evaluation**

<table>
<thead>
<tr>
<th>Thyroid Nodule Workup</th>
<th>Patient Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>0.98</td>
<td>0.4–4.2 μU/mL</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>264</td>
<td>&lt;5 pg/mL</td>
</tr>
<tr>
<td>CEA</td>
<td>96</td>
<td>&lt;4 ng/mL</td>
</tr>
<tr>
<td>FNA</td>
<td>Medullary thyroid carcinoma, positive for all the submitted neuroendocrine markers</td>
<td></td>
</tr>
<tr>
<td>Free metanephrine</td>
<td>2.1</td>
<td>&lt;0.9 nmol/L</td>
</tr>
<tr>
<td>Free normetanephrine</td>
<td>3.3</td>
<td>&lt;0.9 nmol/L</td>
</tr>
</tbody>
</table>

The Table describes the parturient’s initial workup on discovery of the neck mass. The calcitonin and CEA levels were concerning for thyroid carcinoma, which was confirmed by FNA. Elevated metanephrines and normetanephrines raised suspicion for pheochromocytoma. Abbreviations: CEA, carcinoembryonic antigen; FNA, fine needle aspiration; TSH, thyroid-stimulating hormone.

**Figure 1.** Preoperative MRI, identifying nodule in left adrenal gland. The figure demonstrates a nodule in the left adrenal gland (red arrow). MRI, magnetic resonance imaging.

**Anesthetic Management for Posterior Retroperitoneoscopic Adrenalectomy**

Preoperatively, the patient arrived anxious regarding her pending surgeries. The patient requested anxiolytic medications before being taken to the operating room. After a detailed discussion of risks and possible implication on the pregnancy, we initiated a dexmedetomidine load (0.5 μg/kg over 15 minutes) and infusion (0.5 μg/kg/h) in the preoperative area under continuous HR and pulse oximetry monitoring. Once in the operating suite, a pre-induction arterial line was inserted. After an intravenous induction of anesthesia (fentanyl, 100 μg; propofol, 100 mg; rocuronium, 60 mg) in modified rapid sequence fashion, a central venous catheter was placed in the right internal jugular vein. The patient positioning is shown in Figure 2. This position was chosen by the surgical team to allow best retroperitoneal exposure with minimal disturbance of the abdominal cavity. The posterior retroperitoneal approach avoids the surgical manipulations of any intraabdominal organs and is usually faster than the transabdominal technique. Bispectral index monitoring was used for the assessment of anesthetic depth (range, 40–50). General anesthesia was maintained with isoflurane (end-tidal concentration, 0.5–0.9 vol %); nicardipine and dexmedetomidine infusions were titrated for hemodynamic variations associated with tumor manipulation (target: mean arterial blood pressure [MAP] within 15% of baseline, HR within 90–110 bpm). Intravenous fentanyl boluses (50–75 μg) were given intraoperatively (total 300 μg). The surgical procedure was completed in 109 minutes, and the total anesthetic exposure was 135 minutes. The combination of dexmedetomidine, nicardipine, and balanced general anesthesia provided stable hemodynamics during adrenalectomy without severe hypertension or hypotension. There was no need for vasopressor therapy after tumor removal. The patient was extubated in the operating room at the end of the case. Postoperative fetal HR (FHR) monitoring in the recovery room showed normal HR patterns. Overnight, the patient was monitored in the intensive care unit on continuous HR and invasive blood pressure monitoring. The patient was discharged on postoperative day 1 on phenoxybenzamine (10 mg orally twice daily) due to the small remaining contralateral adrenal nodule and the need for a second surgery 1 week later. Labetalol was discontinued.
the dexmedetomidine load and infusion preoperatively as described previously. No additional invasive monitors were used for this surgery. General anesthesia was induced in rapid sequence fashion (fentanyl, 100 μg; propofol, 120 mg; succinylcholine, 100 μg). After endotracheal tube placement, neuromuscular blocking agents were avoided due to the requisite nerve monitoring during the thyroidectomy. General anesthesia was maintained with isoflurane (end-tidal concentration 0.5–0.9 vol %) and an intravenous remifentanil infusion (0.2–0.4 μg/kg/min, total 6 mg). Bispectral index monitoring was used for anesthetic depth assessment (range, 35–50). An intravenous phenylephrine infusion (≤0.5 μg/kg/min) was used to support the blood pressure and titrated to MAP target within 15% of baseline. The surgical procedure was completed in 259 minutes, and the total anesthetic exposure was limited to 295 minutes. The combination of dexmedetomidine, remifentanil, and balanced general anesthesia provided stable hemodynamics during thyroidectomy without severe hypertension. The patient received a total of 4 mg of phenylephrine during the surgical procedure to maintain MAP within 15% from baseline. The patient was extubated in the operating room at the end of the case. Postoperative FHR monitoring in the recovery room showed normal HR patterns. The patient was discharged from the hospital the following day.

The histology of the surgical specimen described multifocal medullary thyroid carcinoma pT2(m)N1b with lymphovascular invasion. The largest nodule was 2.5 cm in diameter.

**Follow-Up/Fetal Outcome**

The parturient continued to receive routine prenatal care throughout the remainder of the pregnancy. Phenoxybenzamine was discontinued after the thyroid surgery. Plasma fractionated metanephrine levels 2 weeks after adrenalectomy and 5 months after surgery were all normal. Calcitonin and carinoembryonic antigen were also within normal 5 months postoperatively. The parturient continued to receive routine prenatal care throughout the remainder of the pregnancy. Phenoxybenzamine was discontinued after the thyroid surgery. Although there is recent evidence that benzodiazepine teratogenicity is overstated and benzodiazepine use during pregnancy may be safe during all phases of pregnancy,9,10 there is still hesitation to use this drug group during pregnancy because of possible implications on fetal brain development.11

**DISCUSSION**

When considering the anesthetic management of adrenalectomy for pheochromocytoma, effective perioperative anxiolysis is critical to prevent increased catecholamine secretion and resultant hemodynamic instability. The tumor-related hemodynamic variables present challenging considerations for the perioperative physician under normal circumstances; however, our patient’s case was complicated by the fact that both tumor resections had to occur during the second trimester of pregnancy. The possibility for catecholamine-driven hemodynamic changes and associated mortality were particularly important for our patient given the potential for an undesirable fetal outcome. Our case presented a particularly exceptional challenge because anxiolytics commonly used in patients with pheochromocytomas, such as benzodiazepines (FDA pregnancy class D), may be associated with unacceptable risk in the parturient. Although there is recent evidence that benzodiazepine teratogenicity is overstated and benzodiazepine use during pregnancy may be safe during all phases of pregnancy,10 there is still hesitation to use this drug group during pregnancy because of possible implications on fetal brain development.11
Dexmedetomidine’s properties would make it the ideal adjuvant anesthetic for a patient with multiple endocrine neoplasia, yet little literature is available regarding its use in parturients.\textsuperscript{1,2}

Dexmedetomidine has been documented to blunt hemodynamic responses in women undergoing cesarean deliveries without adverse fetal outcomes.\textsuperscript{3,13} The placental transfer of dexmedetomidine appears to be low in animal studies, and fetal exposure to dexmedetomidine may be beneficial by providing neuroprotection.\textsuperscript{14} With recent attention given to the impact of general anesthesia on the developing brain, FDA recommendations for obstetric and fetal surgery now include an endorsement to use dexmedetomidine when appropriate.\textsuperscript{12}

Yet, despite this knowledge, scant literature exists regarding its use in parturients undergoing nonobstetric-logic surgical procedures.\textsuperscript{4–6,15} Our case report appears to be the first report of the elective use of dexmedetomidine for abdominal nonobstetric surgery during the second trimester of pregnancy. In addition to anxiolysis, dexmedetomidine may improve perioperative hemodynamic stability by suppressing the pheochromocytoma-related catecholamine release.\textsuperscript{16,17} While pheochromocytoma occurrence during pregnancy appears to be quite rare, the early, expedited diagnosis and control of symptomatology are extremely important for minimizing risk to both mother and fetus.\textsuperscript{18}

Our patient only reported mild symptoms related to pheochromocytoma despite having significant metanephrine levels. The time for hemodynamic optimization varies with symptom severity and is usually guided by the criteria by Roizen et al.\textsuperscript{19} In nonpregnant patients, an average of 4–6 weeks is usually needed for sufficient α-blockade compared to the 13 days we allowed in this case report.\textsuperscript{8} Since our patient did not display the classical pheochromocytoma symptoms (palpitation, sweating, headache) in addition to hypertension, we used only the presence of orthostasis and absence of frequent premature ventricular contractions and ST segment changes to guide the sufficiency of α-blockade.\textsuperscript{20}

It is currently recommended to remove the tumor(s) in the second trimester.\textsuperscript{18} Further, in our patient, the diagnosis of thyroid carcinoma increased the urgency of surgical resection of both endocrine tumors.

The reported case is unique because our patient was exposed twice to dexmedetomidine during her pregnancy. In both surgical procedures, the fetus was exposed to dexmedetomidine via boluses and continuous infusions, totaling 45 μg and 150 μg for each surgery, respectively. While the exact fetal blood concentration of dexmedetomidine in our case is unknown, it may be minimal since the placental transfer of the drug is low.\textsuperscript{13}

There are possible disadvantages for using dexmedetomidine in the perioperative period related to the risk of hypotension and severe bradycardia.\textsuperscript{1} While we did not observe any significant changes in maternal HR, we cannot rule out that dexmedetomidine may have caused fetal bradycardia. We did not use intraoperative FHR monitoring during these surgical procedures because the fetus was seen viable. Based on the recommendations of the obstetric consultants and American College of Obstetricians and Gynecologists guidelines, FHR monitoring was only performed postoperatively.\textsuperscript{21} The threshold for fetal viability is in flux and has been reported as early as 22 weeks of gestation, and additional intraoperative monitoring may be utilized if the parents request premature delivery at signs of fetal distress.\textsuperscript{22} There is no conclusive evidence that FHR monitoring during nonobstetric surgery improves fetal outcome.\textsuperscript{23} Perioperative changes in FHR do not always indicate fetal distress because FHR patterns and lack in variability may be related to general anesthesia.\textsuperscript{24} However, intraoperative monitoring may be advantageous if dexmedetomidine is used at a later stage of pregnancy or if there are concerns for fetal well-being to monitor for fetal bradycardia.

This case report documents that dexmedetomidine can be given in meaningful concentrations for the anesthetic management of pregnant patients undergoing nonobstetric surgery.

\section*{DISCLOSURES}

\textbf{Name:} Amanda L. Faulkner, MD.

\textbf{Contribution:} This author helped provide patient care, conduct the study, analyze the data, and write the manuscript.

\textbf{Name:} Eric Swanson, MD.

\textbf{Contribution:} This author helped provide patient care, conduct the study, analyze the data, and write the manuscript.

\textbf{Name:} Thomas L. McLarney, MD.

\textbf{Contribution:} This author helped provide patient care, conduct the study, analyze the data, and write the manuscript.

\textbf{Name:} Cortney Y. Lee, MD.

\textbf{Contribution:} This author helped provide patient care, conduct the study, analyze the data, and write the manuscript.

\textbf{Name:} Annette Rebel, MD.

\textbf{Contribution:} This author helped provide patient care, conduct the study, analyze the data, and write the manuscript.

\textbf{This manuscript was handled by:} Bobbiejean Sweitzer, MD, FACP.

\section*{REFERENCES}


11. Olutoye OA, Baker BW, Belfort MA, Olutoye OO. Food and Drug Administration warning on anesthesia and brain

\textcopyright 2018 International Anesthesia Research Society. Unauthorized reproduction of this article is prohibited.