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CASE REPORT

Carcinoid tumor and intravenous octreotide infusion during labor and delivery

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ABSTRACT
There are limited numbers of reports concerning the management of pregnancy complicated by carcinoid tumors. Octreotide, the synthetic analogue of somatostatin, has been found to be beneficial in preventing the perioperative exacerbation of carcinoid syndrome. We present a case of the successful use of neuraxial analgesia/anesthesia for labor and vaginal delivery in a symptomatic parturient afflicted with carcinoid syndrome, who received an intravenous infusion of octreotide throughout labor and vaginal delivery.

Keywords: Anesthesia; Obstetrical; Pregnancy complications; Neuroendocrine tumor; Carcinoid; Antineoplastic agents; Hormonal; Octreotide

Introduction

Carcinoid tumors, the most common gastrointestinal endocrine tumors, with frequent metastases,[1] are more commonly found in females, not uncommonly during childbearing age.[2] Approximately five percent of patients with tumors exhibit symptoms of carcinoid syndrome.[1] Therefore, it is not unexpected to find pregnancies complicated by carcinoid syndrome and afflicted parturients presenting as unique challenges to anesthesiologists.

Octreotide, the synthetic analogue of the naturally-occurring hormone somastatin, has been found to be beneficial in preventing exacerbation of these symptoms.[3] We describe a symptomatic parturient who delivered vaginally at term under neuraxial analgesia while receiving a continuous intravenous infusion of octreotide.

Case report

A 43-year-old woman (G2, P0) was diagnosed six years earlier with carcinoid tumor with liver metastasis. Before this pregnancy, and after Yttrium-90 radio-embolization therapy, she continued mostly asymptomatic. During this pregnancy, the patient experienced episodes of lower abdominal cramping, cutaneous flushing, diarrhea, and bronchospasm. All symptoms and signs resolved after intramuscular injections of long-acting octreotide. Electrocardiography and echocardiography were interpreted as normal. In the early third trimester, she was referred to the section of obstetric anesthesiology for an anesthetic plan for delivery.

At 37^{+2} weeks of gestation, the patient was admitted in labor with a history of spontaneous rupture of membranes and regular contractions. She reported a one-week history of increased flushing, diarrhea, abdominal pain, and dyspnea on exertion after earlier discontinuation (without medical consultation) of her octreotide therapy. Her weight was 77 kg and her height 160 cm. Her blood pressure was 130/50 mmHg and pulse 78 beats/min in sinus rhythm. Although she was not in any respiratory distress, chest auscultation revealed bilateral wheezing in all lung fields. Skin flushing was observed.

Peripheral intravenous as well as radial intra-arterial cannulae were placed. Blood was obtained and analyzed for serum electrolytes, blood urea nitrogen and serum creatinine; all results were reported as "normal." Single doses of ranitidine (50 mg) and diphenhydramine (25 mg), as well as octreotide (25 μg/h) were given intravenously. She reported severe pain with her contractions. Analgesia was induced via combined spinal-epidural technique (intrathecal fentanyl 25 μg followed

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by intermittent epidural injections of 0.125% bupivacaine, total 12 mL) and maintained with a continuous infusion (12 mL/h) of a mixture of 0.08% bupivacaine and fentanyl 2 μg/mL. Subsequent auscultation of the lung fields revealed a significant decrease in wheezing.

The first stage of labor was routine; the second stage lasted 150 min, with fetal tachycardia to 180 beats/min and deep variable decelerations over the last 30 min before delivery. A male infant weighing 3.3 kg was delivered vaginally with a compound presentation of a posterior arm relieved by McRobert's maneuver. Apgar scores were 4 and 6 at 1 and 5 min respectively. Analysis of cord blood revealed the following values: umbilical artery pH: 7.08, Pco_2: 57 mmHg, Po_2: 30 mmHg, bicarbonate: 16 mmol/L, base excess: −15.2 mEq/L; umbilical vein pH: 7.11, Pco_2: 40 mmHg, Po_2: 38 mmHg, bicarbonate: 15 mmol/L, base excess: −12.9 mEq/L.

The third stage of labor was completed with manual extraction of the placenta after one 400-μg intraoral spray of nitroglycerine. A third degree perineal laceration was repaired with anesthesia provided by epidural injection of 2% lidocaine.

On the second postpartum day, the patient was given subcutaneous octreotide 150 μg every 8 h and the octreotide infusion was discontinued. On a visit to the nursery, the patient was observed to have severe flushing which soon abated. There were no other detectable signs of carcinoid syndrome. The patient was discharged home the next day.

Discussion

The Institutional Review Board of the University of Maryland does not require patient informed consent for a case report of a single patient who cannot otherwise be identified.

Commonly located in the gut, carcinoid tumor cells secrete numerous hormones (including: serotonin, corticotrophin, histamine, dopamine, substance P, neurotensin, prostaglandins and kallikrein) into the portal vein, where these active substances are inactivated by hepatic metabolism.[4] However, systemic circulation of these hormones, as seen with our patient who had metastases in the liver, leads to the classical signs and symptoms of carcinoid syndrome: cutaneous flushing, diarrhea, abdominal pain and bronchospasm.[1,4,5]

The manifestations of carcinoid syndrome can vary over time. For example, chronic exposure to these hormones (perhaps serotonin and tachykinins) can lead to fibrotic complications of the endocardium of the right heart; patients present with both valvular (tricuspid regurgitation and pulmonic stenosis/regurgitation) and right ventricular dysfunction.[6–8] An acute, severe, even life-threatening form of carcinoid syndrome, carcinoid crisis, is heralded by severe hypo- (rarely hyper-) tension and bronchospasm. The release of vasoactive peptides into the circulation most likely is the cause of carcinoid crisis,[2] and can be precipitated with the administration of anesthesia. Excessive sympathetic outflow accompanying induction and emergence from anesthesia or the use of drugs that are known triggers of carcinoid tumor cell secretion, such as vasoactive amines, are also possible causes.[9]

Drugs that block the peripheral effects of these hormones (corticosteroids, serotonin antagonists, histamine-receptor anatagonists,[8] kallikrein inactivators,[6] non-adrenergic vasopressors[10]) have been employed in the management and prevention of carcinoid crises. However, the mainstay for prevention and treatment of carcinoid crises is octreotide, a somatostatin-analogue that binds to the somatostatin receptor subtypes 2 and 5.[11] Octreotide exhibits pharmacologic effects similar to the natural hormone somatostatin, including secretory inhibition of some anterior pituitary hormones, suppression of pancreatic endocrine and exocrine function, inhibition of gastric acid and gastrointestinal hormone secretion, and suppression of serotonin secretion.[12]

Currently, intramuscular injections of long-acting octreotide (instead of regular octreotide) are used in the treatment of chronic carcinoid symptoms.[13] Octreotide levels rise sharply after the first injection but subsequently fall, reaching a nadir at about seven days, then rise slowly reaching a plateau at 14 days, and remain elevated for the entire month.[1] During subsequent injections, there is no nadir but rather a steady level for the entire month. It is suggested that patients who are receiving long-acting octreotide for the first time should have surgery delayed until two weeks after the first injection, unless regular octreotide is given as a supplement. It is suggested that intravenous octreotide infusions be available when anesthesia and surgery are planned.[2]

In our case there was no diagnostic dilemma when the parturient presented complaining of cutaneous flushing, diarrhea and bronchospasm, since metastatic carcinoid disease had already been diagnosed and confirmed by bioassay (elevated urinary 5-hydroxyindoleacetic acid, the breakdown product of serotonin).[14] Our patient tolerated an ablative radio-embolic procedure and, importantly, demonstrated a positive response to octreotide. Recent echocardiography had already confirmed "normal" cardiac status. However, our plan was formulated to prevent a carcinoid crisis while providing routine obstetric analgesia or anesthesia. Therefore, our goals were to: treat a symptomatic patient with intravenous octreotide, provide maternal (invasive vs. non-invasive) monitoring appropriate to her pathophysiologic state, provide excellent labor analgesia to blunt a "hyperadrenergic" stress response, maintain normovolemia with hydration and, if needed, prepare for abdominal delivery with a plan for neuraxial as well as general

anesthesia. General anesthesia, if necessary, would be conducted while avoiding known drug triggers and blunting the "hyper-adrenergic" stress response seen on induction and emergence.

When the patient was admitted to the labor and delivery suite with a one-week history of diarrhea, blood and serum chemistry was checked for any electrolyte imbalance. Intravenous access was initiated to provide hydration and, because the patient was already exhibiting wheezing and cutaneous flushing, an intravenous infusion of octreotide was administered. The dose of octreotide, of up to 100 μg/h, should be titrated to clinical effect,[14] as octreotide-related side-effects (e.g., irregular heart beats, hyperglycemia, diarrhea, headache, etc.) may occur.[11] Diphenhydramine and ranitidine, two drugs not uncommonly used in the care of the parturient, were administered to decrease any further effects of histamine release.

Continuous electrocardiography was instituted and a radial artery cannula inserted to assess beat-to-beat hemodynamic function, in anticipation of the need to titrate the rate of octreotide infusion or to infuse other vasoactive drugs if the patient's physiologic status suddenly deteriorated. A central line was considered, to avoid the risk of a dislodged peripheral intravenous catheter with abrupt discontinuation of the octreotide infusion, but the patient refused it. Intravenous infusions of inotropic and vasopressor agents such as epinephrine, norepinephrine, dopamine or ephedrine are discouraged because they may stimulate tumor mediator release.[15] With the patient receiving octreotide, our standard vasopressor agent for obstetric anesthesia, a dilute phenylephrine infusion, was believed appropriate to treat any possible episode of maternal neuraxial anesthesia-induced hypotension (which never occurred).

There are numerous reports of successful administration of neuraxial anesthesia and general anesthesia for surgical patients without hemodynamic compromise while receiving octreotide therapy,[1] typically for resection of an abdominal mass; this situation is dissimilar to childbirth in an awake patient. A neuraxial anesthesia-induced sympathectomy in the setting of endocrine-induced vasodilatation[1] might cause severe hypotension, tissue and fetal hypoperfusion and reflex vasoactive amine release, a trigger for further tumor cell secretion.[2,9] Some clinicians have preferred epidural to spinal anesthesia for patients with carcinoid syndrome, believing that spinal anesthesia is contraindicated because of its more pronounced effect on sympathetic innervation; others disagree.[16,17] It is possible that octreotide therapy and the attenuation of hormonal-induced vasodilatation make this argument moot.

For our laboring patient already receiving intravenous octreotide, we selected combined spinal-epidural technique to provide what we considered to be optimal labor analgesia without compromising hemodynamic stability, while it could be intensified for operative anesthesia. Hypotension was minimized by intravenous co-hydration and uterine displacement, and by using intrathecal fentanyl initially, followed later with moderate doses of dilute epidural local anesthetic and opioids.

Had operative delivery been required, we would have extended the in-situ epidural blockade; however, if general anesthesia was required, our plan was to avoid drugs associated with histamine-release (e.g., thiopental morphine, atracurium) and to provide adequate blunting of the pressor-response to tracheal intubation and extubation using remifentanil.[18]

Octreotide is approximately two-thirds bound by maternal protein,[19] and the unbound fraction is believed to cross the placenta by passive diffusion.[20] Two recent reviews of prolonged octreotide use in pregnancy warn of possible intrauterine growth restriction,[21,22] although reproductive toxicity from the use of octreotide has not been reported.[11,22,23] In our case, the neonate was born with a mild metabolic academia, which could have been related to abnormalities of the fetal heart rate (fetal tachycardia with recurrent deep variable decelerations) observed in the last 30 min of labor and a difficult delivery. In the post-partum period, the patient was closely monitored for exacerbation of her symptoms and signs; the octreotide infusion was continued.

In conclusion, we present the case of a patient with known hepatic metastases of a carcinoid tumor who was admitted in term labor with cutaneous flushing and wheezing after discontinuing her octreotide therapy. A continuous intravenous infusion of octreotide was initiated and the patient tolerated labor and vaginal delivery under neuraxial analgesia without further complications.

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