Quetiapine and Refractory Hypotension During General Anesthesia in the Operating Room

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Quetiapine is an atypical antipsychotic with known α-adrenergic antagonism. We present a case of refractory hypotension that occurred after induction of general anesthesia in a patient being treated with quetiapine. This patient was not currently taking antihypertensives and had no known cardiovascular abnormalities. We observed that the hypotension was most responsive to vasopressin. We recommend further investigation regarding the interaction of quetiapine and general anesthesia. (Anesth Analg 2013;117:641–3)

An increasing number of patients presenting for surgery are being treated with multiple medications for their depression. Atypical antipsychotics are commonly being prescribed as adjunct therapy for major depressive disorders. Quetiapine is a well-tolerated second-generation atypical antipsychotic used to treat schizophrenia, bipolar disease, and more recently, major depressive disorder (Table 1, Ref. 1). It is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT_{1A}$ and $5HT_2$, dopamine D_1 and D_2, histamine H_1, and adrenergic α_1 and α_2 receptors (Table 1, Ref. 2). The half-maximal inhibitory concentration (IC_{50}) value for receptor antagonism is most pronounced at the H_1 receptor followed by α_1, $5HT_2$, α_2, D_2, $5HT_1$, and D_1, respectively.[1] Quetiapine has no appreciable affinity for cholinergic muscarinic or benzodiazepine receptors and has a lower affinity for D_2 receptors than conventional antipsychotics.[2] Reduced D_2 affinity may explain why quetiapine causes fewer extrapyramidal side effects and is generally well tolerated.[2]

In placebo-controlled clinical trials, 4% of patients experienced postural hypotension (Table 1, Ref. 2). Postural hypotension was also one of the most common side effects in elderly patients, with a 13% rate of occurrence.[3] Quetiapine's antagonism of adrenergic α_1 receptors may explain postural hypotension observed with this drug (Table 1, Ref. 1). Complications of hypotension include syncope, transient ischemic attack, stroke, myocardial infarction, and death.[4] Caution has been advised when combining quetiapine with other centrally acting drugs and with antihypertensive drugs (Table 1, Ref. 1).

We cared for a patient taking quetiapine, lamotrigine, and venlafaxine who experienced refractory hypotension (>20% decrease in the systolic blood pressure (BP) from baseline for >10 minutes) and exhibited a weakened response to ephedrine, phenylephrine, and vasopressin during general anesthesia. We reviewed electronic records and noted the unedited automated recordings of the noninvasive BPs. We have obtained IRB approval to query an existing electronic database for anesthesia records.

CASE REPORT

A 35-year-old woman, 113 kg, 64 inches tall, ASA physical status III, with a body mass index of 43 kg/m^2, was scheduled for a revision septoplasty. She had not consumed anything since midnight before surgery, other than her morning doses of lamotrigine 300 mg, quetiapine 300 mg, and venlafaxine XR 300 mg. She was not taking any antihypertensive medications. The review of her cardiac systems was normal. Preoperatively her arterial BP was 123/92 mm Hg, and heart rate was 90 beats per minute.

The patient was premedicated with IV midazolam 2 mg and fentanyl 100 μg. Standard monitors were placed, including BP cuff, pulse oximetry, and electrocardiography. Her BP immediately before induction was 102/45 mm Hg (Fig. 1). Anesthesia was induced with IV fentanyl 50 μg, lidocaine 80 mg, and propofol 200 mg. The patient was paralyzed with succinylcholine 120 mg. Anesthesia was maintained with an oxygen/air mixture and desflurane up to 6%.

Within 5 minutes of induction, the patient's BP decreased to 49/30 mm Hg. This was initially treated with boluses of ephedrine in 10 mg increments and boluses of phenylephrine in 200 μg increments. This was also treated with infusing 1 L lactated Ringer's solution over 30 minutes. The desflurane was decreased to approximately 5%. These interventions increased her BP from the nadir after induction to approximately 80/31 mm Hg. However, since the patient only modestly responded to continued boluses of ephedrine and phenylephrine, we administered vasopressin in boluses of 4 units. The combination of phenylephrine and vasopressin restored her BP to 80 to 90 mm Hg per 30 to 40 seconds. Over the course of 2 hours, the patient received 40 mg ephedrine, 1500 μg phenylephrine and 20 units vasopressin boluses.

DISCUSSION

The differential diagnoses for hypotension in this case include cardiovascular depression, myocardial ischemia, and anaphylaxis. Cardiovascular depression from the combination of propofol and fentanyl may have contributed to the initial nadir in BP. All volatile anesthetics cause myocardial depression. However, there is no mechanism by which

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Table 1. Web Sites Cited

Reference	Web Site
1	AstraZeneca Pharmaceuticals LP. Seroquel. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/20639se1-017,016_seroquel_lbl.pdf. Accessed July 10, 2011.
2	AstraZeneca Pharmaceuticals LP. Highlights of prescribing information. Available at: http://www1.astrazeneca-us.com/pi/Seroquel.pdf. Accessed July 10, 2011.
3	Available at: dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=53c3e7ac-1852-4d70-d2b6-4fca819acf26. Accessed December 5, 2011.
4	DailyMed. Available at: http://dailymed.nlm.nih.gov/dailymed/druglnfo.cfm?id=58356#nlm34090-1. Accessed December 6, 2011.
5	DailyMed. VASOPRESSIN injection. Available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=54454. Accessed December 6, 2011
6	Center for Disease Control and Prevention. Overweight and Obesity. Available at: http://www.cdc.gov/obesity/data/trends.html. Accessed December 5, 2011.

desflurane should impair the vasoconstrictive properties of ephedrine and phenylephrine.[5] There was no electrocardiographic evidence of myocardial ischemia or history to suggest that the patient was at risk of coronary artery disease. We considered anaphylaxis unlikely, given the lack of other signs of anaphylaxis (bronchoconstriction, rash, edema). However, anaphylactic markers such as serum tryptase were not drawn.

Hypotension after induction of general anesthesia is not uncommon. In fact, predictors of hypotension postinduction have been identified in the literature.[6] These include ASA III to IV, baseline mean BP <70 mm Hg, 50 years or older, propofol as the induction drug, and high induction dosages of fentanyl.[6] Only the use of propofol is applicable to our patient.

Refractory hypotension in patients receiving general anesthesia in the presence of quetiapine has not been described. However, clozapine, another atypical antipsychotic, has been found to cause refractory hypotension under general anesthesia.[7] Several reports have described hypotensive episodes with overdoses of quetiapine that have been effectively treated with intralipids.[4,8–10] Quetiapine's antagonism of adrenergic α_1 receptors may explain the postural hypotension observed with this drug (Table 1, Ref. 1). Postural hypotension is a more common adverse effect with second-generation antipsychotics than first-generation antipsychotics.[4] Among the second-generation class, clozapine and quetiapine have the highest incidence of postural hypotension, followed by iloperidone, lurasidone, and asenapine.[4]

The patient was also taking venlafaxine and lamotrigine. There have been no case reports of these drugs precipitating adverse reactions during anesthesia. Venlafaxine is a selective serotonin norepinephrine reuptake inhibitor in the phenothylamine class of antidepressants and is prescribed for depression, anxiety, and panic disorders. It is a potent inhibitor of neuronal serotonin and norepinephrine reuptake, and a weak inhibitor of dopamine reuptake. Venlafaxine has no significant affinity for muscarinic, histaminergic, or α_1-adrenergic receptors. Venlafaxine sustained release has

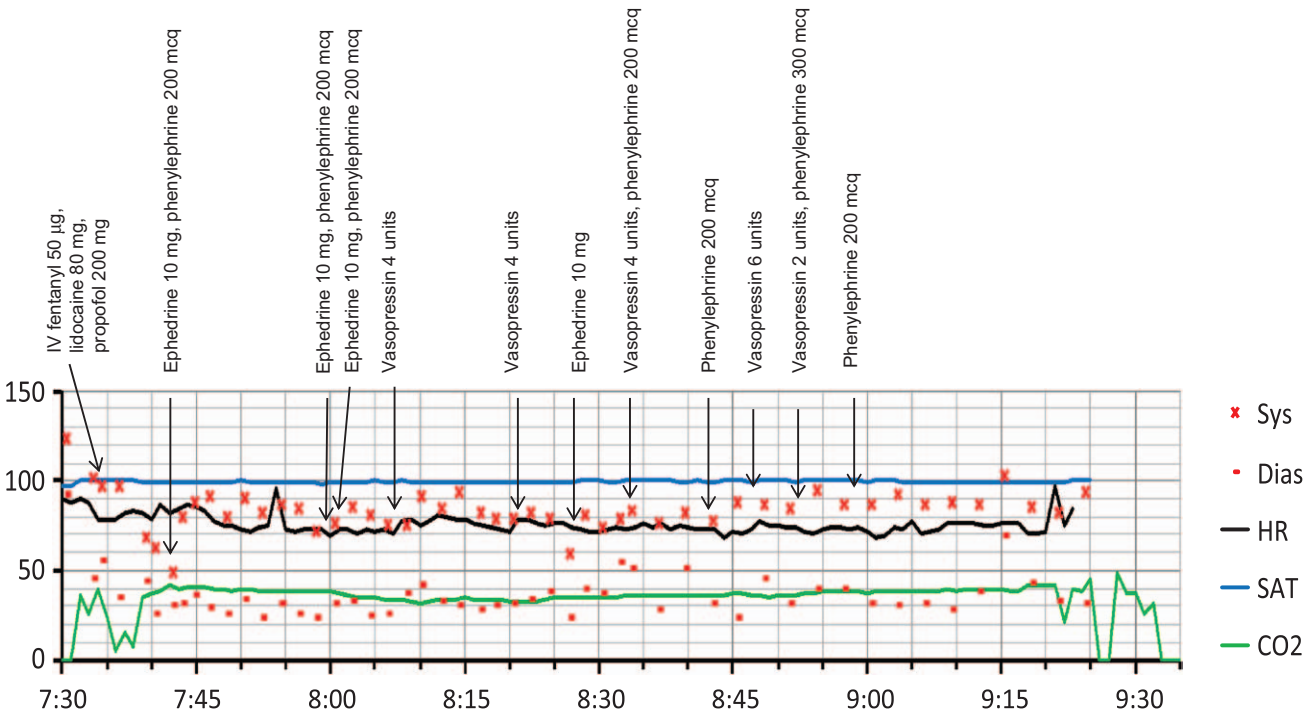

Figure 1. Timing of vital signs and medication administration. Sys = systolic blood pressure; Dias = diastolic blood pressure HR = heart rate; Sat = oxygen saturation; CO2 = end-tidal carbon dioxide levels.

been associated with sustained diastolic hypertension in approximately 3% of patients, but it is more common with the immediate release venlafaxine. Nausea, headaches, and dizziness are the most common side effects. Based on this information, venlafaxine was most likely not the cause of the patient's refractory hypotension (Table 1, Ref. 3).

Lamotrigine is an anticonvulsant medication used for seizures and bipolar disorders. The exact mechanism of action is unknown, but lamotrigine does affect sodium channel receptors and may weakly inhibit serotonin $5HT_3$ receptors. It has very little affinity for adrenergic, dopaminergic, γ-aminobutyric acid, histaminic, and muscarinic receptors. Lamotrigine's side effects include serious skin rashes and multiorgan hypersensitivities. It can infrequently cause hypertension, flushing, syncope, and postural hypotension. Based on its weak affinity for serotonin $5HT_3$ receptors, lamotrigine was most likely not responsible for the patient's refractory hypotension as well (Table 1, Ref. 4).

Vasopressin is a neurohypophyseal hormone that inhibits diuresis and is a potent vasoconstrictor. Vasopressin constricts arterioles by binding to V_1 receptors. These receptors are coupled to G proteins and the phospholipase IP3 pathway. Vasopressin has only weak vasoconstrictive affinity for the pulmonary arterioles, and therefore is the drug of choice for vasoconstriction in patients with pulmonary hypertension (Table 1, Ref. 5).

One third of adults and 17% of children in the United States are morbidly obese (Table 1, Ref. 6). Morbidly obese patients in the supine position may experience postural hypotension due to compression of the vena cava and decreased venous return. With a body mass index of 43 kg/m^2, morbid obesity may have contributed to our patient's refractory hypotension in the supine position. However, her BP in the supine position before induction was 102/45 mm Hg. Some would argue that oscillometric BP measurements might not be accurate in obese patients.[11] Interestingly enough, 1 study shows that a person's weight is not a determining factor in the accuracy of oscillometric BP readings. Thus, obesity itself may not influence the true measurement of BP.[12]

Ephedrine and phenylephrine were not very effective in restoring our patient's BP, most likely because the patient was α-blocked by quetiapine. Vasopressin seems to have contributed to sustaining a viable BP but not as well as expected. One case report describes the use of vasopressin to restore BP in a patient receiving clozapine.[7]

We report a case in which refractory hypotension occurred after induction of general anesthesia in a patient treated with quetiapine, venlafaxine, and lamotrigine. The hypotensive episodes were modestly refractory to ephedrine, phenylephrine, vasopressin, and crystalloid boluses. Caution may be warranted when planning anesthesia for patients treated with quetiapine.

DISCLOSURES

Name: Katherine A. Poole, MS.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Katherine A. Poole approved the final manuscript.
Name: Nina Weber, MSN.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Nina Weber approved the final manuscript.
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Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Michael Aziz approved the final manuscript.
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