CASE REPORT

Hypotension Following Cardiac Surgery Associated with Paroxetine and Mirtazapine Withdrawal

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This case describes a 15-year-old patient who experienced postoperative hypotension following an elective Ross procedure for aortic stenosis/insufficiency. The patient was taking paroxetine and mirtazapine for depression which were held prior to surgery. Hypotension occurred approximately eight hours postoperatively and required vasopressor support. Upon reinitiation of antidepressant therapy, hypotension resolved and vasopressor support was discontinued. A year later the patient required conduit replacement, and antidepressant therapy was weaned off during the three weeks prior to surgery. No hypotension was observed following the second surgery. Paroxetine withdrawal has been well-documented within adult literature, but there is little information regarding mirtazapine withdrawal. Furthermore, cardiovascular effects have not been well-documented, and even less is known within the pediatric population. Withdrawal symptoms in these agents may be explained by cholinergic rebound and/or rapid decline in serum concentrations upon abrupt discontinuation. It may be reasonable to consider tapering antidepressants with short half-lives prior to elective surgery in which patients may not be able to take maintenance medications for more than 24 hours.

KEYWORDS antidepressants, hypotension, mirtazapine, paroxetine, thoracic surgical procedures

J Pediatr Pharmacol Ther 2008;13:25-28

Paroxetine is a psychotropic medication belonging to the class of drugs commonly known as selective serotonin (5HT) reuptake inhibitors (SSRIs). *In vitro* animal data suggests that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake with limited effects on norepinephrine and dopamine reuptake. Additionally, paroxetine has limited affinity for muscarinic-, alpha$_1$-, alpha$_2$-, beta-, dopamine (D_2)-, 5HT$_1$-, 5HT$_2$-, and histamine (H_1)-receptors.[1] Mirtazapine, on the other hand, is believed to antagonize central presynaptic alpha$_2$ inhibitory receptors, resulting in increased central serotonin and norepinephrine activity. Additionally, mirtazapine is a potent antagonist of 5HT$_2$-, 5HT$_3$-, and H_1-receptors and a moderate antagonist of muscarinic and peripheral alpha$_1$-receptors.[2] Paroxetine withdrawal syndrome has been well-documented within the adult literature.[3-13] With the exception of neonatal abstinence, there is only limited knowledge of paroxetine withdrawal symptoms in pediatric

ABBREVIATIONS 5HT, serotonin; RV-PA, right ventricular-to-pulmonary artery; SSRI, selective serotonin reuptake inhibitor; TEE, intraoperative transesophageal echocardiography

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patients and there is little information regarding mirtazapine withdrawal. Cardiovascular effects associated with withdrawal of these agents have not been well-documented, and even less is known within the pediatric population. We describe a case of an adolescent who experienced significant postoperative hypotension following withdrawal of paroxetine and mirtazapine.

CASE

The patient is a 15-year-old male with a history of aortic stenosis/insufficiency who had become increasingly symptomatic during the year prior to surgery. He also had a history of mild obesity, migraine headaches, and depression for which he was treated with oral paroxetine (Seroxat, Paxil; GlaxoSmithKline, Triangle Park, NC) 25 mg daily and mirtazapine (Remeron; Organon USA Inc., Roseland, NJ) 15 mg every evening. The patient and family elected to undergo a scheduled Ross procedure for his aortic valve disease. The operation was relatively uneventful, except for some posterior suture line bleeding which prolonged the procedure and required reinitiation of cardiopulmonary bypass to control the bleeding. Hemostasis was achieved, and the patient left the operating room without any significant hemorrhage. Cardiopulmonary bypass and aortic cross-clamp times were 329 and 232 minutes, respectively, and biventricular function and autograft function were both excellent as determined by intraoperative transesophageal echocardiography (TEE).

The patient did well for the initial 8 hours after surgery. The patient was maintained on milrinone 0.5 μg/kg/min and nitroglycerin 1 μg/kg/min. Systolic blood pressures (mmHg) were kept in the 90s and mean arterial blood pressures in the 60s to safeguard against further bleeding.

At approximately 8 hours postoperatively, the patient became hypotensive with a fairly rapid drop in systolic blood pressure to 50-60 mmHg and mean arterial pressures in the low 40's. Nitroglycerin was discontinued, and he was given volume resuscitation. The patient was unresponsive to dopamine titrated to 10 μg/kg/min. An epinephrine infusion was then initiated and titrated to 1 μg/kg/min without marked effect on his blood pressure. TEE showed hyperdynamic function with good function of the aortic (autograft) valve, and tamponade was ruled out after bedside opening of the sternotomy incision. Norepinephrine was then initiated with a positive effect on his blood pressure and was titrated up to 0.4 μg/kg/min. Epinephrine was rapidly weaned off, and dopamine was weaned to 2.5 μg/kg/min. The norepinephrine maintained his systolic blood pressure in the 90-100 mmHg range and was able to be weaned to 0.05 μg/kg/min 8 hours later. Because of concerns for withdrawl, paroxetine and mirtazapine were restarted the evening of postoperative day 1, approximately 20 hours after onset of the hypotensive episode. The norepinephrine was eventually weaned off 60 hours after the original hypotensive episode. The patient progressed well, was discharged from the hospital on postoperative day 8, and recovered from his cardiac surgery.

One year postoperatively, the right ventricular-to-pulmonary artery (RV-PA) conduit became stenotic and required replacement. At this time, the patient was still maintained on paroxetine but was no longer taking mirtazapine. Due to concerns regarding his previous postoperative hypotension, the paroxetine was weaned off during the three weeks prior to surgery with weekly dose reductions. The patient underwent repeat open heart surgery to replace the RV-PA conduit, and the surgery was uneventful without any episodes of cardiovascular instability. The patient was relatively tachycardic (120-140 bpm) for the first 72 hours after surgery; otherwise, his postoperative course was without complications. The patient did not experience any hypotension and was discharged on postoperative day 4. Paroxetine was then restarted after surgical follow-up.

DISCUSSION

Case reports and studies of paroxetine withdrawal syndrome have been well-documented within the adult literature, with one of the most commonly reported symptoms being lightheadedness or dizziness.[3-13] Investigation of cardiovascular parameters was conducted in only one study.[12] Michelson and colleagues found that patients treated with paroxetine had a statistically significant increase in stand-

ing heart rate and orthostatic change in heart rate after abrupt paroxetine discontinuation; however, no changes were found in supine or standing blood pressure.[12]

There is only limited knowledge of paroxetine withdrawal symptoms in pediatric patients (excluding neonatal abstinence), with only one case reported in the literature.[14] In this instance, a nine-year-old boy with major depressive disorder developed a syndrome of dizziness, drowsiness, headache, fatigue, and emesis approximately 24 hours after abrupt discontinuation of paroxetine 10 mg twice daily. He subsequently was restarted on the same dose with resolution of symptoms within 24 hours. He was uneventfully tapered off paroxetine over a period of 4 weeks several months later.[14]

The explanation behind paroxetine withdrawal syndrome has not been fully elucidated; however, two main theories exist, one of which is attributed to cholinergic rebound and the other to serotonin withdrawal. Since paroxetine has some cholinergic receptor affinity, cholinergic rebound may very well explain symptoms such as nausea and emesis, diarrhea, diaphoresis, restlessness, insomnia, and malaise.[15] Severe cholinergic rebound could account for symptoms such as dizziness, lightheadedness, and ataxia which have been pervasive among patients experiencing withdrawal; however, since paroxetine has only limited cholinergic receptor affinity, this potential may also be limited. For this reason, paroxetine's pharmacokinetic parameters are believed to play a substantial role in development of symptoms related to serotonin withdrawal. With a parent half-life of approximately 21 hours in adult patients and no active metabolites,[1,16] synaptic serotonin withdrawal may occur rapidly (within 24-48 hours) upon abrupt discontinuation of paroxetine. Pediatric patients may clear paroxetine even more rapidly and have an average paroxetine half-life of approximately 11 hours (2.6 to 21.1 hours).[17] While there has been limited information regarding paroxetine withdrawal in children and adolescents, this data suggest they may be at an increased risk for earlier symptoms due to more rapid drug clearance upon discontinuation.

With regards to mirtazapine, there have been only two case reports of withdrawal symptoms noted within the adult literature[18,19] and no reports among pediatric patients. Adult pharmacokinetic studies have shown a parent compound half-life ranging from 20 to 40 hours, with younger adults having a half-life at the lower end of this range.[2,20] Additionally, metabolites of mirtazapine account for only 5% to 10% of biological activity.[20] There are no data regarding pharmacokinetic parameters in children and adolescents, and the half-life may be even shorter in this population. Considering mirtazapine's pharmacokinetic parameters, it is also reasonable that serotonin withdrawal effects may be seen upon abrupt discontinuation. Additionally, since mirtazapine is a moderate antagonist of muscarinic receptors, cholinergic rebound may be more likely to occur than with paroxetine.

To date, there have been no reports of cardiovascular events related to paroxetine or mirtazapine withdrawal in adult or pediatric patients. It is possible that our patient's postoperative hypotension could be attributed to a withdrawal syndrome induced by the concurrent abrupt cessation of two separate antidepressant medications. Additionally, our patient's history of aortic stenosis/insufficiency along with the cardiovascular stress associated with his surgical procedure may have been predisposing factors for cardiovascular-associated withdrawal symptoms, especially with the use of two medications with the potential to induce cholinergic rebound or serotonin withdrawal upon abrupt cessation. While it cannot be determined whether tapering his paroxetine and/or being on a single antidepressant prevented any events related to his second surgery, they do support a withdrawal theory in relation to his first postoperative course. From this experience, it may be reasonable to consider tapering antidepressants with relatively short half-lives (≤ 24 hours) prior to elective surgery in which it is expected that a patient may not be able to take his or her maintenance medications for more than 24 hours. Additionally, in the case of unplanned procedures, resumption of maintenance antidepressants should be considered in the early postoperative course. At the very least, health care practitioners should be aware of symptoms associated with antidepressant withdrawal syndromes, including potential cardiovascular symptoms in high-risk patients, and be diligent in observing for their occurrence.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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