Olanzapine-induced hyperventilation: case report

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Although olanzapine therapy has been associated with fewer extrapyramidal side effects than the traditional antipsychotic medications, reported side effects include dystonia, tardive dyskinesia, hypotension, diabetes mellitus, seizures and neuroleptic malignant syndrome. There are no previous published reports of hyperventilation associated with olanzapine therapy, but we present the case of a male patient who developed dyspnea and hyperventilation while taking olanzapine.

Même si l'on établi que la thérapie à l'olanzapine provoque des effets secondaires extrapyramidaux moins nombreux que ceux des médicaments antipsychotiques traditionnels, les effets secondaires signalés comprennent la dystonie, la dyskinésie tardive, l'hypotension, le diabète, les convulsions et le syndrome malin des neuroleptiques. On n'a pas signalé auparavant d'hyperventilation reliée à la thérapie à l'olanzapine, mais nous présentons le cas d'un homme qui a eu des crises de dyspnée et d'hyperventilation pendant qu'il prenait de l'olanzapine.

Introduction

Olanzapine is a novel antipsychotic medication used for the treatment of psychoses, schizophrenia, schizoaffective disorders, bipolar disorders and other conditions with psychotic or delusional components.[1,2] It has been associated with fewer cases of extrapyramidal side effects than the traditional antipsychotic medications such as haloperidol and fluphenazine.[3] It does, however, have other serious side effects including dystonia, tardive dyskinesia, hypotension, diabetes mellitus, seizures and neuroleptic malignant syndrome.[2] Our literature search did not reveal any reports of hyperventilation associated with olanzapine treatment, but we present a case in which a male patient developed hyperventilation after he began taking olanzapine.

Case report

A 30-year-old single male who was diagnosed with schizoaffective disorder according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), had been prescribed various tricyclic antidepressants and selective serotonin reuptake inhibitors in the past, but these were discontinued because, in the patient's words, "they stopped working." He then started taking mirtazapine (15 mg at bedtime), which he found to be effective. He was also prescribed typical antipsychotic medications for episodes of para-

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noia, but these medications were discontinued when symptoms improved. The patient also met the DSM-IV criteria for heroin dependence in full remission. He was enrolled at a local methadone maintenance clinic and was prescribed methadone (110 mg/day). The patient did not have a history of any other psychiatric disorder, but he did have hepatitis C, which he contracted several years earlier, a hip fracture from a car accident 10 years earlier and a benign testicular tumour for which he underwent partial orchiectomy several years earlier. He also had asthma as a child, but it had been stable for several years without ongoing treatment.

During the course of treatment, the patient again began to engage in self-reflective thinking and experience paranoid fears that people were staring at him or constantly thinking and talking about him. He also had persistent, intrusive, negative thoughts about family members having fatal accidents; he reported insomnia due to the intrusive thoughts and complained of being increasingly depressed.

After ruling out other medical or substance-induced causes, various treatment options were explored. The patient continued to take mirtazapine and agreed to start taking the atypical antipsychotic medication olanzapine (5 mg at bedtime). Over the next few days, he reported feeling less paranoid and inquired about increasing the olanzapine dose further. After possible side effects were discussed, the olanzapine dose was increased to 10 mg at bedtime. The patient's paranoia decreased and his sleep improved, but he continued to have difficulty leaving the house during the day because of excessive fear for his safety. He had not reported any side effects with olanzapine, and, to achieve optimal benefits of the olanzapine, the dosage was increased to 5 mg in the morning and 10 mg at bedtime. Mirtazapine was continued at the same dosage.

The patient continued to do well until the third month of olanzapine therapy when he experienced severe psychosocial stressors, which worsened his paranoia and anxiety. The intrusive thoughts returned, he became increasingly paranoid around people and his sleep deteriorated to about 2–3 hours per night. He reported taking his medications faithfully and denied using any illicit substances. (This was confirmed through drug screening at the methadone clinic.) The dose of olanzapine was increased further to 5 mg in the morning and 15 mg at bedtime. This brought him some relief from insomnia, but he continued to feel anxious and paranoid.

To augment the effects of olanzapine, various other therapeutic options were discussed. The patient agreed to start taking gabapentin (300 mg, 3 times a day), and the mirtazapine was tapered and eventually discontinued. The following week, he reported anxiolytic effects of gabapentin, but the paranoia, social isolation and intrusive thoughts continued. He requested that the dosage of olanzapine be increased again. After a long discussion about the risks and benefits, the dosage of olanzapine was increased to a total of 25 mg/day in divided doses.

The patient responded to the increase, and the improvement continued for 1 week. At that time, he started to complain of sedation and difficulty breathing. Knowing he had a history of childhood asthma, an internal medicine consult was sought. As well, the gabapentin dosage was decreased to 100 mg, twice daily, and 300 mg at bedtime. However, his breathing difficulties, characterized by gasping for air, continued. He also felt very anxious and restless. The patient was advised to go to the emergency room but, when contacted, he said that he felt too paranoid to go to the hospital. Instead, he stopped all his medications and stayed home. He left the house only once the next day to obtain his methadone, and he returned home immediately. Toward the end of the day, he felt that his shortness of breath had improved.

When he returned to the clinic, he suggested that the hyperventilation and breathing difficulty may have been caused by his medications because the symptoms stopped when he stopped taking the medications. However, the paranoia and intrusive thoughts also returned. Because gabapentin was the last medication added to his regimen, it was tapered and discontinued. He resume taking olanzapine at 20 mg/day in divided doses. Another attack of breathing difficulty caused him to stop taking olanzapine again. He became paranoid and was very skeptical of trying a new medication. After a long discussion, he agreed to take olanzapine at a reduced dosage (5 mg twice a day, with an extra dose if needed), but, even at this dosage, he continued to have bouts of breathing difficulty. He found that a lower dosage of olanzapine (5 mg at bedtime) did not cause any difficulty breathing.

The patient described this difficulty breathing or dyspnea as restlessness and a strong urge to breathe heavily. He also experienced chest discomfort and was unable to relax. This feeling would last 8–10 hours.

The patient reluctantly saw his primary care physi-

cian, but the physician's evaluation did not reveal any new medical conditions to account for the hyperventilation and dyspnea. The laboratory test results were as follows: sodium, 143 mmol/L, potassium, 4.2 mmol/L, chloride 98 mmol/L (low), bicarbonate 28.8 mmol/L, calcium 2.47 mmol/L, blood urea nitrogen 4.6 mmol/L UREA, creatinine 88.4 μmol/L, glucose 4.9 mmol/L, globulin 46 g/L, alkaline phosphatase 105 U/L, serum glutamic oxaloacetic transaminase (SGOT) 56 U/L and serum glutamic pyruvic transaminase (SGPT) 93 U/L. His leukocyte count was 9.5×10^6/L, hemoglobin 145 g/L, platelets 237×10^9/L, mean corpuscular volume 93 fL. His thyroid stimulating hormone level was 0.71 mU/L. Hepatitis profile was positive for hepatitis C, with a viral load of 360 000 U/mL. His alpha-fetoprotein level was 3.4 μg/L, serum iron level 21 μmol/L and serum iron binding capacity was 62 μmol/L. Test results for autoimmune disorders were negative. Results of chest and abdominal computed tomography and a spirometry evaluation were negative.

After being explained the risks and benefits of various medications, the patient agreed to try risperidone. The initial dosage of 1 mg twice a day was eventually increased to 2 mg twice a day. This reduced his paranoia without causing dyspnea or hyperventilation.

Discussion

Hyperventilation with olanzapine therapy has not been previously reported in the medical literature. Although proving causality is difficult, the experience of respiratory symptoms at higher doses of olanzapine, improvement after discontinuation and recurrence of these symptoms with rechallenge of olanzapine suggests a causal association.

Several medications including adenosine,[4] salicylates,[5,6] progestin[7] and quetiapine[8] have been implicated in dyspnea. The mechanism by which these medications induce hyperventilation is not entirely clear, but it is thought to involve a direct action on the respiratory centre in the midbrain and an indirect action through the central and peripheral chemoreceptors and neurotransmitters such as serotonin.[4–7] Shelton et al[8] described a case of hyperventilation with quetiapine administration and suggested serotonergic involvement. Olanzapine may induce hyperventilation and dyspnea in a similar fashion.

Serotonin can modulate respiration through both central and peripheral chemoreceptors. Olson and colleagues[9] found that serotonin depletion in rats can lead to hyperventilation. A potent tryptophan hydroxylase inhibitor, para-chlorophenylalanine, depleted whole brain serotonin levels and led to an increased rate of breathing. Quetiapine, a novel antipsychotic, produces a central serotonergic blockade which persists at 50% of serotonin receptors for up to 26 hours.[8,9] Olanzapine is a selective monoaminergic antagonist as well, with high affinity for 5-$HT_{2A/2C}$ receptors.[2] Therefore, it is possible that olanzapine, at a high dosage, may block these serotonin receptors and induce hyperventilation.

Another possible explanation of olanzapine-induced hyperventilation may be the phenomenon of respiratory dyskinesia.[10,11] This is considered a variant of tardive dyskinesia involving the respiratory muscles in which dyskinetic movements of the respiratory muscles such as the diaphragm may present clinically as dyspnea, shortness of breath, forceful breathing and hyperventilation.[10,11] However, these dyskinesias usually develop after long-term exposure to antipsychotic medications and may persist for some time after the cessation of drug treatment.[12] Our patient developed these side effects shortly after the olanzapine dosage was increased and stopped having these symptoms when the dosage was lowered. This, therefore, does not support a diagnosis of tardive respiratory dyskinesia.

The hyperventilation may have been an akathisia-like extrapyramidal side effect. Akathisia generally develops shortly after the onset of treatment with antipsychotic agents and remits with their discontinuation. Hirose et al[13] described 5 cases of "respiratory akathisia" with the administration of antipsychotic agents. Patients developed hyperventilation and dyspnea soon after starting their antipsychotic medications and improved quickly after they stopping taking them. Patients described having an inner sense of restlessness that was relieved by heavy forceful breathing.[13] This is similar to what our patient described as his subjective experience and breathing response. Further, his pattern of breathing responded to the discontinuation and subsequent rechallenge of olanzapine. Our patient was able to tolerate 5 mg/day without any breathing disturbances. It is possible that he was experiencing akathisia that was abated at lower doses of olanzapine. A trial of an anticholinergic agent or a beta-adrenergic antagonist (usual treatment for akathisia) may have aided with this explanation, but this was not explored with our patient. Moreover, olanzapine has anticholinergic effects as well,[2] which could explain the lower incidence of akathisia with olanzapine.

Our patient was also taking methadone and gabapentin when he started hyperventilating. There are no reports of any direct interaction between olanzapine and either of these medications. Although the metabolism of olanzapine is complex, it is primarily metabolized by the cytochrome P-450 system (CYP-450), mostly by the isoenzyme 1A2 system and 2D6,[2] whereas methadone is metabolized primarily by the CYP-3A4 system.[14] Gabapentin is not metabolized by the liver and is excreted through renal mechanisms.[15] Further, gabapentin has no known plasma protein binding.[16] Olanzapine and methadone have some protein binding.[17] There have not been any published reports of these drugs displacing each other from the plasma binding protein sites thereby affecting each other's serum levels. There may be some yet unexplained interaction between olanzapine and methadone, but if this caused higher serum levels of methadone, the resulting effect should be a decrease in the respiratory drive because of methadone's depressant effects on the respiratory centre, not increased respiratory drive leading to hyperventilation and dyspnea.[18] If, however, olanzapine decreased methadone levels, the resulting hyperventilation could be explained by possible methadone withdrawal. If that were the case, the patient should then have complained of other opiate withdrawal symptoms as well. Therefore, it appears to unlikely that such a mechanism was involved.

Conclusion

Olanzapine is an atypical antipsychotic agent with known side effects that include sedation, weight gain, hyperglycemia, orthostatic hypotension and rare incidences of seizures.[2] Olanzapine can also cause elevations in serum transaminase levels, especially in the presence of hepatitis C, as was the case with our patient.[2] However, this is the first report to suggest that olanzapine, at a high dosage, may cause hyperventilation and dyspnea.

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