Case Report

Aripiprazole Overdose Causing Neuroleptic Malignant Syndrome: A Clinical Report and Brief Review

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ABSTRACT

A student on aripiprazole (an atypical second generation antipsychotic drug) was admitted with deliberate overdose of the drug, and in the course of her hospital stay developed a clinical picture of mild neuroleptic malignant syndrome (NMS). She survived after supportive care.

A brief review is included on the incidence of NMS secondary to aripiprazole overdose, and reveals an increasing incidence.

Key Words: Aripiprazole, Antipsychotic drug, Drug overdose, Neuroleptic malignant syndrome, NMS

Introduction

The Case: A 22-year-old female student was brought to the casualty department of a major teaching hospital with a history of consumption of 11 tablets of aripiprazole (15 mg each; total dose 165 mg) 5 hours prior to admission. On admission she was drowsy, but oriented and normally responsive. She reported excessive sleepiness, heaviness in the head and a mild sense of imbalance. There was no history of spontaneous vomiting, nausea, abdominal pain, visual disturbance or loss of consciousness. The student had been regularly taking aripiprazole tablets 15 mg twice daily for the preceding 2–3 months, as prescribed by her psychiatrist. Prior to this she had been taking risperidone. At the hospital where she had been first taken, she was administered salt water to induce vomiting, as she refused stomach wash.

On physical examination, the patient appeared drowsy. All vital parameters were normal except for mild tachycardia. Pupils were normal, and there was no sign of cranial nerve dysfunction. There was no evidence of nystagmus. No focal deficits or abnormal movements could be detected, and her gait was normal. Cardiorespiratory and abdominal examinations were unremarkable.

Upon admission to the ICU, her saturation was 97% and heart rate was 96 bpm. Blood haematology and routine biochemistry were normal.

Within 4 hours of admission, the patient developed fever in the range of 102–104^{0}F, not responding to antipyretics. There was no evidence of muscle rigidity or tenderness. Serum creatine phosphokinase was mildly elevated (320 IU/L). Urine examination and tests for malarial parasites were negative. Liver enzymes were not elevated. The EKG revealed no rhythm disturbance. There was no clinical or laboratory evidence of infection; however, a broad-spectrum antibiotic was initiated as treatment for fever.

The patient recovered and was discharged after 48 hours, with appropriate advice from the psychiatrist. The clinical diagnosis was possible neuroleptic malignant syndrome secondary to acute aripiprazole overdose.

Discussion

Clinical management of psychosis has undergone a sea change in the last few decades. Before the 1950s, psy-

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chiatrists had only sedatives in their armamentarium to calm patients during periods of agitation. The introduction of the first antipsychotic agents (chlorpromazine and haloperidol) in the early 1950s revolutionized the treatment of schizophrenia, bipolar disorders and other major psychoses. The shortcomings associated with the early antipsychotics comprised severe side effects such as neuroleptic malignant syndrome, extra-pyramidal syndromes, and akathisia. This led to the development of the second generation of antipsychotics (also known as atypical antipsychotics), some examples of which include clozapine, olanzapine and risperidone. Though comparatively less than the typical antipsychotics, nevertheless these drugs too had significant side effects including somnolence, weight gain, glucose intolerance, dyslipidaemia, increased QTc interval, and myocarditis.[1]

In 2002, the Food & Drugs Administration (FDA), USA, approved aripiprazole as a new atypical antipsychotic. It is classified as a serotonin and dopamine system stabilizer, and belongs to the third generation of antipsychotics.[2]

Aripiprazole has a high affinity for, and is a partial agonist of the dopamine D_2 receptor. As a partial agonist, aripiprazole functions as a dopamine system stabilizer. It reduces dopaminergic neurotransmission when such activity is excessive, and enhances it when such activity is deficient. This restores dopamine neurotransmission to the normal range.[3] Likewise, it also has a serotonin system stabilizer effect. In therapeutic doses, aripiprazole ameliorates the positive and negative signs and symptoms of schizophrenia, and has a very favourable side effect profile, making it the most prescribed antipsychotic among psychiatrists, in the current decade.

The most common adverse effects associated with the use of aripiprazole include headache, nausea, vomiting, constipation, insomnia, lightheadedness, and somnolence, anxiety, agitation, akathisia, and tremor. It is claimed to be the antipsychotic with the lowest side effect profile equal to that of a placebo.[4]

A total of 76 cases of deliberate or accidental overdose with aripiprazole have been reported worldwide up to the time of preparing this case report. These include overdoses with aripiprazole alone, as well as in combination with other substances. No fatality has been reported in these cases. Of the 44 cases with known outcome, 43 recovered without any sequelae, while one recovered with some sequelae (mydriasis and feeling "abnormal"). The largest known acute ingestion with a known outcome involved 1080 mg of aripiprazole (36 times the maximum recommended daily dose) in a patient who fully recovered.[5] Of late, data is accumulating that neuroleptic malignant syndrome could be caused by second and third generation antipsychotics, including aripiprazole even at therapeutic doses.[6]

There is no specific antidote or treatment modality for aripiprazole overdose. ECG monitoring and other biochemical monitoring is recommended, and treatment must be undertaken to address any disturbances in these.

Neuroleptic Malignant Syndrome (NMS): After anaesthetic drugs, the most common cause for neuroleptic malignant syndrome is antipsychotic drug therapy. When antipsychotics are administered in overdose, they generally block dopamine receptors in genetically susceptible individuals.[7] The estimated incidence of NMS with conventional antipsychotics is reported to be 0.02–2.44%.[8]

Signs and symptoms of NMS include high fever not responding to antipyretics, confusion, altered sensorium, excessive sweating, muscular rigidity, autonomic imbalance, seizures, coma and death. Aripiprazole, like other antipsychotics, has been reported to cause neuroleptic malignant syndrome, when administered in larger than therapeutic doses. However, when compared to other antipsychotics, the incidence is significantly less. During pre-marketing surveillance, there were two cases of possible NMS reported. The disorder typically develops within two weeks of starting the therapy, but can occur at other times as well. If muscular rigidity and/or tremors are significant, serum creatine phosphokinase will be elevated. Arterial blood gas analysis may reveal a metabolic acidosis without anion gap. ECG may reveal a QT interval prolongation.

Active treatment is not required in most cases of NMS induced by aripiprazole. Ventilatory and circulatory support along with drugs like dantrolene, sodium bromocriptine, and apomorphine, in combination with electroconsvulsive therapy suffice to eliminate fatal outcome. Benzodiazepines are also useful.

Conclusion

While newer (second and third generation) atypical antipsychotics are being accepted worldwide as the treatment of choice in most major psychiatric disorders, it is worthwhile remembering and looking for side effects,

including neuroleptic malignant syndrome, which are normally associated with typical antipsychotics.

REFERENCES

1. Freedman R. Schizophrenia. N Engl J Med 2003; 349:1738–1749.
2. Stahl SM. Dopamine system stabilizers, aripiprazole, and the next generation of antipsychotics. Part 1: Goldilocks actions at dopamine receptors. J Clin Psychiatry 2001; 62(11): 842–842.
3. Taylor DM. Aripiprazole: A review of its pharmacology and clinical use. Int J Clin Pract 2003; 57(1): 49–54.
4. Levine M, Traub S, Burns MJ. The pharmacology and toxicology of aripiprazole. Int J Med Toxicol 2004; 7(1): 5–11.
5. Abilify (aripiprazole): Overdosage and contraindications. RxList: The Internet Drug Index. http://www.rxlist.com/abilify-drug.htm.
6. Marshall PB, Mellman TA, Nguyen SXC. Neuroleptic malignant syndrome with addition of aripiprazole to olanzapine. Am J Psychiatry 2008 November; 165:1488–1489.
7. Gurrera RJ. Sympathoadrenal activity and the etiology of neuroleptic malignant syndrome. Am J Psychiatry. 1999 Feb, 156(2): 169–180.
8. Ananth J, Parameswaran S, Gunatilake S, Burgoyne K, Sidhom T. Neuroleptic malignant syndrome and atypical antipsychotic drugs. J Clin Psychiatry. 2004 April; 65(4): 464–70.