Ziprasidone and Hypokalemia: A Case of 2 Predisposing Factors for QTc Prolongation Without Development of Torsades de Pointes

Sir: Although concerns about sudden cardiac arrhythmia death associated with the use of an antipsychotic drug actually predate the description of torsades de pointes, it is this fatal arrhythmia and its electrocardiographic (ECG) predictor (corrected QT [QTc] interval prolongation) that have become of increasing concern related to the use of antipsychotic medications during recent years. The first case reports of patients dying from a fatal arrhythmia while taking an antipsychotic medication appeared in 1963,[1] and 3 years later torsades de pointes was described.[2] Although it would be some years before these 2 phenomena were linked, with similar cases mounting,[3] the reality of antipsychotic medication–induced torsades de pointes has since become an entity that those prescribing these medications must guard against.

Torsades de pointes is a term that refers to polymorphic ventricular tachycardia that occurs in the setting of an abnormally long QT interval.[4] The most common cause of this arrhythmia is treatment with a drug that prolongs the QT interval.[5] The QT interval is an ECG measurement that encompasses both depolarization and repolarization of the ventricle. Depolarization of the ventricle is primarily due to rapid influx of sodium ions through sodium channels, and its duration is represented electrocardiographically by the QRS interval. Repolarization, the duration of which is represented by the ST segment, involves sodium, potassium, and calcium channels. Although altering either of these components can yield arrhythmias, some antipsychotic medications prolong the QT interval through their effects on repolarization.[6] More specifically, it is through a potassium channel that drug-induced QT prolongation is achieved. This potassium channel is the potassium rectifier channel (I Kr).[7] Therefore, drugs that block the I Kr channel can induce QT prolongation and subsequent sudden cardiac death from torsades de pointes in otherwise healthy patients.[8] Given this effect, QT intervals should be followed when patients are treated with medications that can significantly prolong the QT interval. Since the QT interval shortens with increasing heart rate, it is usually corrected for heart rate, and this corrected interval is known as the QTc interval.[9] An absolute QTc interval greater than 500 msec, or an increase of 60 msec from baseline, is a surrogate marker for the ability of a drug to cause torsades de pointes.[10]

Although for many years the antipsychotic drug of most concern in this realm was thioridazine, in 1996 a new atypical antipsychotic, sertindole, was not registered in the United States because it prolonged the QTc interval and was associated with 12 sudden unexplained deaths in Europe.[11,12] These concerns arose again when ziprasidone showed a modest effect on QTc interval during clinical trials.[13] During these studies, patients treated with ziprasidone showed a QTc interval increase of 20.3 msec from baseline. Although this prolongation was somewhat less than that produced by thioridazine (35.6 msec), enough concern developed surrounding ziprasidone that it initially became common practice among many physicians to check baseline and periodic ECGs when employing ziprasidone therapy. While this practice has waned with time, concerns remain in the psychiatric community about ziprasidone's QTc effects.

As previously mentioned, QT-prolonging drugs are the most common cause of torsades de pointes; however, other factors such as congenital long QT syndromes and electrolyte abnormalities can also prolong the QT interval and induce torsades de pointes. Hypokalemia is the most notable of QT-prolonging electrolyte abnormalities.[4] Even modest hypokalemia with potassium levels in the range of 2.8 to 3.5 mmol/L has been shown to prolong the QTc interval to 660 msec.[14] Although hypokalemia has been shown as an independent variable to be a significant inducer of QTc prolongation and torsades de pointes, it also has been noted to trigger torsades de pointes in patients with other QTc prolongation issues. For example, hypokalemia was noted to trigger torsades de pointes in some groups of individuals with congenital long QT syndrome.[15] Further, experimental models have shown that the pharmacologic blockade of I Kr by antiarrhythmics such as quinidine and dofetilide is increased proportionally with decreasing potassium concentrations.[16] Given the above, it would be of both clinical concern and interest if a patient who was taking full-dose ziprasidone were to present with hypokalemia.

Case report. Mr. A, a 54-year-old white man, had a history significant for chronic paranoid schizophrenia, chronic obstructive pulmonary disease, and hypertension. He presented on January 31, 2002, with a 36-hour history of progressive muscle weakness that began in his lower extremities and over the course of a day progressed to include his upper extremities as well as his neck and face. On presentation, his physical examination results were pertinent for diffuse, symmetrical extremity weakness (3/5), decreased deep tendon reflexes, and loss of gag reflex, but intact sensation. His cardiac and pulmonary examination results were unremarkable, but he was noted to report some right upper quadrant pain (later discovered to be due to cholelithiasis). He specifically denied a history of flu-like symptoms, nausea, vomiting, or loss of bowel or bladder control. The patient further denied any recent vaccinations, diuretic abuse, laxative abuse, or licorice ingestion.

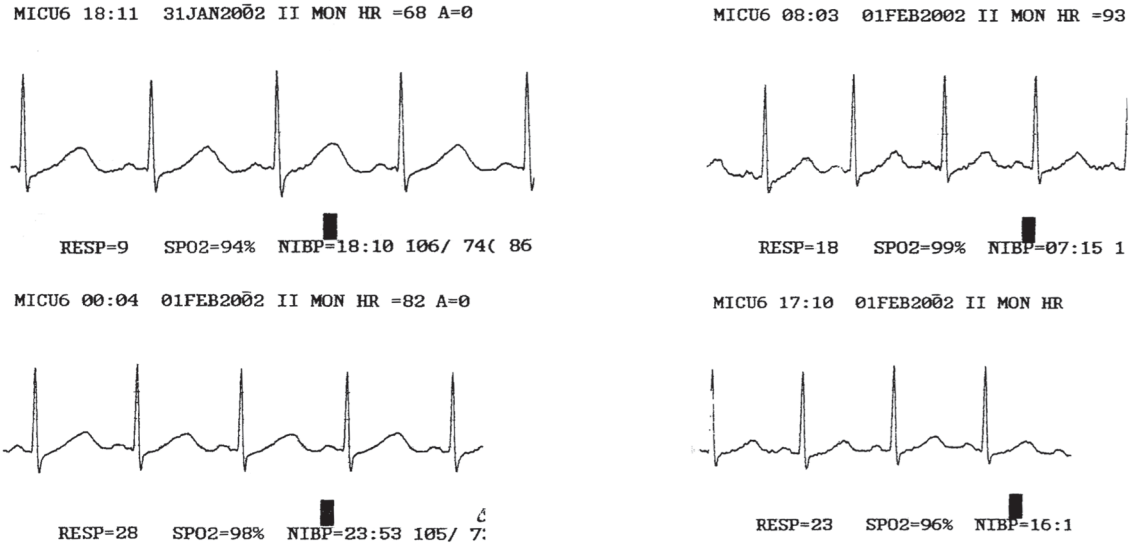
Mr. A was known to have a baseline ECG normal sinus rhythm with a QT interval of 400 msec and QTc interval of 440 msec. His medications on admission included olanzapine 10 mg q.h.s., naproxen 250 mg b.i.d., propranolol 20 mg t.i.d., clonazepam 2 mg t.i.d., zolpidem 20 mg q.h.s., benztropine 1 mg b.i.d. p.r.n., ranitidine 150 mg b.i.d., docusate sodium 100 mg b.i.d., albuterol metered-dose inhaler 2 puffs q4 p.r.n., fluticasone nasal spray 42 μg 2 puffs b.i.d., and ziprasidone 80 mg b.i.d. Mr. A had begun ziprasidone treatment in April 2001 and had been taking the dose of 80 mg b.i.d. since June 2001. His initial laboratory findings were pertinent for profound hypokalemia with a presenting potassium level of 2.0 mmol/L. He was also noted to be in rhabdomyolysis, presumably from hypokalemia, with an initial creatine phosphokinase (CPK) level of 3583 U/L.

Mr. A was admitted to the medical intensive care unit for cardiac monitoring and treatment of his hypokalemia. His initial telemetry showed sinus rhythm at a heart rate of 68, QT interval of 520 msec, and QTc interval of 550 msec. Over the course of 24 hours, his potassium level was corrected to 3.9 mmol/L, and his QT and QTc intervals normalized (Table 1, Figure 1). Ziprasidone treatment was stopped at admission and restarted on February 2, 2002, at the time of hospital discharge. The patient also regained his gag reflex as well as his strength throughout all extremities.

Table 1. Corrected QT (QTc) Interval and Serum Potassium Concentration Over Time in a Ziprasidone-Treated Patient With Hypokalemia and QTc Prolongation

Date	Time	QT Interval (msec)	QTc Interval (msec)	R-R Interval (msec)	Heart Rate	Potassium Level (mmol/L)	Elapsed Time
Jan 31, 2002	18:11	520	550	880	68	2.4	0
Feb 1, 2002	00:04	440	500	760	82	2.5	5 h 53 min
Feb 1, 2002	08:03	400	480	680	93	3.9	13 h 52 min
Feb 1, 2002	17:10	400	480	680	90	3.9	22 h 59 min

Figure 1. Electrocardiogram Tracings in a Patient With Hypokalemia on Ziprasidone Treatment



During his hospitalization, Mr. A was never noted to develop torsades de pointes. Further, his continuous cardiac monitoring never displayed U waves, pauses, or lability of QT interval in either space or time. He was treated appropriately for rhabdomyolysis, and his CPK levels trended toward normal. His potassium level was stabilized, and hypokalemia did not return prior to discharge. Of note, the origin of his hypokalemia was vigorously investigated, but never discovered, and to date he has had no similar recurrence.

This case demonstrates the lack of development of torsades de pointes as well as the degree of QTc prolongation in a patient taking full-dose ziprasidone with profound hypokalemia. Further, it demonstrates the lack of development of ECG factors that are seen with prolonged QT interval prior to the development of torsades de pointes. These factors are known to include the development of U waves, pauses, QT interval lability, and QT dispersion (prolongation) greater than 120 msec from baseline.[4] While our patient's QTc interval was prolonged to a peak of 550 msec, the interval did not approach the degree of prolongation in other patients with similar hypokalemia[14] who were not taking drugs associated with inducing QT prolongation.

The most significant conclusion that can be drawn is that this patient had neither torsades de pointes nor torsades de pointes indicators with the combination of ziprasidone treatment and profound hypokalemia. The cause of the QTc prolongation is difficult to identify with any certainty. It could be argued that it was most likely due to the hypokalemia given that it resolved with the corresponding normalization of the patient's potassium level (Table 1). In addition, the greatest resolution of the prolonged QTc interval was during the first 4 hours of treatment. This observation also argues for hypokalemia as the primary cause given that ziprasidone, though it was stopped at admission, has a half-life of 2 to 5 hours[17] and the patient had been at steady state for some time prior to this event. Certainly, a counter argument can be made that ziprasidone was a contributing factor given that the QTc interval was still 40 msec above baseline even after the patient's potassium level had returned to 3.9 mmol/L (Table 1).

The limitations of this case report are both the initial discontinuation of ziprasidone and the inability to define with clarity the cause of the QTc prolongation. Studies under controlled circumstances would be required to elucidate these boundaries. However, no torsades de pointes or torsades de pointes ECG indicators, with the exception of isolated prolonged QTc interval, were seen in this profoundly hypokalemic patient who was also taking full-dose ziprasidone. Of note, despite the fact that ziprasidone was reinitiated, follow-up ECGs were not obtained. Therefore, we cannot fully assess the independent effect of the antipsychotic on this patient's cardiac conduction.

Dr. Albanese has received honoraria from AstraZeneca and has been on the speakers/advisory boards of Pfizer, Eli Lilly, Forest, and Janssen. Dr. Simpson reports no financial affiliation or other relationship relevant to the subject matter of this letter.

REFERENCES

1. Kelly HG, Fay JE, Lavery SG. Thioridazine hydrochloride (Mellaril): its effects on the electrocardiogram and a report of two fatalities with electrocardiographic abnormalities. Can Med Assoc J 1963;89: 546–554
2. Dessertenne F. Ventricular tachycardia with two variable opposing foci [in French]. Arch Mal Coeur Vaiss 1966;59:263–272
3. Fowler NO, McCall D, Chou TC, et al. Electrocardiographic changes and cardiac arrhythmias in patients receiving psychotropic drugs. Am J Cardiol 1976;37:223–230
4. Roden DM. A practical approach to torsade de pointes. Clin Cardiol 1997;20:285–290
5. Mellaril (thioridazine). Physicians' Desk Reference. 54th ed. Montvale, NJ: Medical Economics; 2000:1108–1110
6. Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. Am J Psychiatry 2001;158:1774–1782
7. DuBuske LM. Second-generation antihistamines: the risk of ventricular arrhythmias. Clin Ther 1999;21:281–295
8. Witchel HJ, Hancox JC. Familial and acquired long QT syndrome and the cardiac rapid delayed rectifier potassium current. Clin Exp Pharmacol Physiol 2000;27:753–766
9. Scheidt S. Basic Electrocardiography. 2nd ed. West Caldwell, NJ: CIBA-GEIGY Pharmaceuticals Publishing; 1993:14–15
10. Haddad PM, Aderson IM. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. Drugs 2002;62:1649–1671
11. Barnett AA. Safety concerns over antipsychotic drug, sertindole. Lancet 1996;348:256–257
12. Sertindole NDA 20-644. Rockville, Md: Food and Drug Administration, Psychopharmacological Drugs Advisory Committee; 1996
13. FDA Briefing Document for Zeldex Capsules (Ziprasidone). New York, NY: Pfizer Inc; 2000:116
14. Curry P, Fitchett D, Stubbs W, et al. Ventricular arrhythmias and hypokalemia. Lancet 1976;2:231–233
15. Berthet M, Denjoy I, Donger C, et al. C-terminal HERG mutations: the role of hypokalemia and KCNQ1-associated mutation in cardiac event occurrence. Circulation 1999;99:1464–1470
16. Yang T, Roden DM. Extracellular potassium modulation of drug block of I Kr: implications for torsade de pointes and reverse use dependence. Circulation 1996;93:407–411
17. Ziprasidone. Mosby's Drug Consult. St Louis, Mo: Mosby Publishing Inc; 2003:3309–3315

B. Rush Simpson, M.D.
Robert P. Albanese, Jr., M.D.
Internal Medicine and Psychiatry
Medical University of South Carolina
Charleston, South Carolina