

LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their thrice-weekly rounds, Dr. Huffman and Dr. Stern discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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QTc Prolongation and the Use of Antipsychotics: A Case Discussion

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Do you wonder about the risk of torsades de pointes (TdP) when you give intravenous (IV) haloperidol to a patient with delirium? Are you concerned about QT interval prolongation in your patients who receive antipsychotics?

Practitioners of medicine and psychiatry are cautioned increasingly about the potential of psychotropic medications to alter the electrocardiogram (ECG) and to produce ventricular arrhythmias. However, the prevalence and nature of cardiovascular side effects and electrocardiographic changes associated with specific antipsychotics are not easily discerned. The following brief clinical vignette and discussion describe our (still-limited) understanding of these relationships. A list of appended references follows the discussion.

Case Presentation

Mr. A, a 61-year-old man with coronary artery disease (CAD) and chronic obstructive pulmonary disease, was admitted to the intensive care unit (ICU) for respiratory failure. He was intubated on admission to the hospital; fortunately, his pulmonary function improved, and he was extubated on the third hospital day. Following extubation, he became agitated, and psychiatric consultation was requested. Delirium was diagnosed and IV haloperidol was recommended. Despite knowing that Mr. A's ECG revealed a normal rate and rhythm, that his QTc was 440 ms, and that the rest of his cardiac intervals were normal, the medical resident was uncomfortable with the recommendation. The resident noted that he had seen "lots of problems" with IV haloperidol and that he would rather not use it to treat Mr. A since he had CAD.

What Is the QT Interval?

How Is It Related to TdP and Other Cardiac Arrhythmias?

The QT interval is an electrocardiographic measure of both depolarization and repolarization within the heart. It is measured as the distance between the beginning of the QRS complex and the end of the T wave. The QRS complex represents ventricular depolarization, while the distance from the end of the QRS to the end of the T wave represents repolarization within the heart. The length of the QT interval decreases as heart rate increases, so, a "corrected" QT value, the QTc, is used to assess the conduction status within the heart.

The QT interval of healthy persons is generally around 400 ms; the QT interval in women is usually about 20 ms longer than that of men. QTc values greater than 450 ms are roughly considered to be "borderline prolonged." QTc values greater than 500 ms are considered prolonged and appear to be associated with an increased risk of arrhythmias, including TdP. It should be noted that the QT interval is "only at best modestly associated with TdP, but despite its difficulties is the best predictor available (p. 1775)."¹

TdP is a malignant polymorphic ventricular arrhythmia with a characteristic pattern seen on the ECG.² It can be the result of a genetic long QT syndrome, but it is often associated with drugs that lengthen the QTc. Such drugs include a number of cardiac medications (e.g., quinidine-type compounds—the class IA antiarrhythmics), antibiotics or antifungals (e.g., erythromycin and ketoconazole), and other medications (e.g., quinine). A number of medications (e.g., cisapride and terfenadine) have been removed from the market because they have been strongly associated with TdP; many others remain available.

In addition to QTc prolongation, other factors that appear to be associated with an elevated risk of TdP include abnormal levels of electrolytes. Potassium, sodium, and calcium are associated with repolarization; hypokalemia, in particular, appears to be associated with an elevated risk of drug-associated TdP. Depleted magnesium also appears to be associated with an elevated risk of TdP. Other risk factors for TdP include systemic diseases (such as hypothyroidism, renal dysfunction, or hepatic disease), central nervous system disturbance (such as cerebrovascular accident or intracranial hemorrhage), cardiac disease (such as ischemic heart disease, congestive heart failure, bradycardia, and conduction delay), and female gender.³

What Effects Do Antipsychotic Medications Have on the QTc?

It appears that all antipsychotic medications can lengthen the QTc. A study of the effects of antipsychotics on the QTc of 154 healthy persons (mostly young men with QTc values in the normal range) found that different antipsychotics increased mean QTc values to varying degrees.⁴ In this study,⁴ medications were titrated to the highest dose tolerated for each drug; mean increases in QTc values are included in Table 1. However, it is difficult to extrapolate the results of this study⁴ to the use of antipsychotics in patients with delirium. First, delirious patients may be unable to describe discomfort from side effects; therefore, the doses used in delirious patients may be higher than those used in the subjects cited in Table 1. Second, delirious patients are often older, have more comorbid medical conditions, have more risk factors for arrhythmia, and are more likely to be taking other medications that may interact with antipsychotics to extend the QT interval. Finally, increases in the QTc were detected following use of oral preparations of antipsychotics; the effects on the QT interval after use of an antipsychotic intravenously may be different or greater than with the oral preparation.

Which Antipsychotics Are Associated With TdP?

Despite the documentation of prolonged QT intervals with all of the above-mentioned antipsychotics, signifi-

Table 1. Effects of Orally-Administered Antipsychotics on the QT Interval^a

Drug	Mean Increase in QTc (ms)	% of Subjects With > 60 ms Increase in QTc
Thioridazine	35.8	29
Ziprasidone	20.6	21
Quetiapine	14.5	11
Risperidone	10.0	4
Olanzapine	6.4	4
Haloperidol	4.7	4

^aData adapted from the U.S. Food and Drug Administration's Center for Drug Evaluation and Research, Psychopharmacological Drugs Advisory Committee.⁴

cant evidence of TdP is linked only to use of thioridazine (and possibly other low-potency antipsychotics), droperidol, and haloperidol. Among antipsychotics, thioridazine is most closely associated with TdP. Other low-potency antipsychotic medications may also be associated with TdP; however, thioridazine, unlike the other low-potency antipsychotic medications, acts as a calcium-channel blocker, and it may be this property that leads to elevated rates of TdP.

Haloperidol has been associated with TdP when given orally or intravenously. At least 2 dozen cases of TdP have been documented with intravenous haloperidol.^{1,5} However, it should be noted that intravenous haloperidol is used extensively throughout the United States and is often administered to patients who are profoundly ill and who may be taking other QT-prolonging medications. So, while there is a risk of TdP with haloperidol, the risk of inducing TdP in any given patient appears to be quite low, especially if other potential risk factors (like abnormal levels of potassium and magnesium, a prolonged QT interval at baseline, and the coadministration of medications) are considered.

Recently, droperidol received a “black box warning” for its association with TdP, despite the fact that the number of reported episodes of TdP was relatively small, considering the extent of its use in the medically ill. A recent review of intramuscular droperidol used for agitated patients found no adverse dysrhythmic effects in over 10,000 patients.⁶ There is, as yet, no known association between the atypical antipsychotics (including ziprasidone and olanzapine) and TdP. Further study and more prolonged use of these medications is required before definitive conclusions can be drawn.

It should be noted that QT prolongation with a single antipsychotic does not necessarily predict QT prolongation with another agent. On the psychiatric consultation service at Massachusetts General Hospital, when the use of IV haloperidol led to QT prolongation, IV droperidol was often substituted for haloperidol; in almost all cases, the substitution did not lead to further prolongation of the QT interval. Similarly, a switch from droperidol (when it caused

QT prolongation) to haloperidol was also accomplished safely and usually without inducing QT prolongation. However, IV droperidol is now rarely used in our institution because of the above concerns about QT prolongation and because of the precautions required for its use.

What Are Other Cardiovascular Effects of Antipsychotic Medications?

Orthostatic hypotension, as a result of α_1 -receptor blockade, can result from the use of low-potency typical antipsychotics, as well as from use of clozapine, risperidone, or quetiapine. Other atypical antipsychotics and high-potency typical agents have a lower rate of orthostatic hypotension; usually this side effect develops only when the patient is significantly volume-depleted. Orthostasis can be profound when antipsychotics are combined with vasodilatory or antihypertensive drugs.

Tachycardia, as a result of anticholinergic effects, may also result from use of low-potency typical antipsychotics, clozapine, and, to a lesser degree, olanzapine. When these medications are combined with other anticholinergic medications, tachycardia can increase or lead to arrhythmias. Therefore, in general, it is best to avoid low-potency antipsychotic medications in patients with cardiac disease, given their propensity to lengthen the QT interval and to cause orthostasis and tachycardia.

Is It Reasonable to Use IV Haloperidol in the Treatment of Mr. A?

Yes. Mr. A was suffering from an acute confusional state that required rapid and effective treatment. Given that the IV route is the most rapid means of administration of an antipsychotic, as well as the most reliable in a person unable to take oral medications, the IV route should be strongly considered. Haloperidol (although not approved for IV use by the Food and Drug Administration) has a long-standing record of efficacy in the symptomatic treatment of delirium when administered intravenously; empiric dosing can be used to find a dose that rapidly reduces a patient's agitation and confusion. Intravenous administration of haloperidol, as opposed to the oral or intramuscular routes of administration, has a negligible rate of extrapyramidal side effects, which avoids the burden of this side effect and foregoes the use of concomitant anticholinergic medications.

With regard to Mr. A's cardiac status, his QTc was not markedly prolonged. As with all patients receiving IV haloperidol, the QTc should be monitored for QT prolongation. However, neither Mr. A's history of cardiac disease nor the baseline QTc of 440 ms were contraindications to the use of haloperidol in this setting. To further reduce the risk of arrhythmia in Mr. A, serum potassium should have been maintained at or above 4 mEq/L and magnesium at or above 2 mEq/L.

If the QT interval had become significantly lengthened (e.g., > 500 ms, or increased by 60 ms), a number of other options would have been available. If Mr. A was able to open his mouth, wafers of olanzapine or risperidone could have been dissolved. If he was able to swallow, any of the antipsychotics could have been administered. Intravenous administration of benzodiazepines could also have been used for sedation; however, these agents can worsen confusion or disinhibition in delirious patients and therefore should be used cautiously.

Drug names: clozapine (Clozaril and others), droperidol (Inapsine and others), erythromycin (Benzamycin Pak, Eryc, and others), haloperidol (Haldol and others), ketoconazole (Nizoral, Ketozole, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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ANNOTATED BIBLIOGRAPHY

Review Articles

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—A very detailed, clearly-written chapter that encompasses virtually all classes of psychotropic medications, with cogent descriptions of their dosing and side effects, as well as a discussion of their use related to special issues in the medical setting. The chapter includes extensive discussions of antipsychotics and their cardiovascular side effects (e.g., the risk of TdP).
- Cassem NH, Murray GB. Delirious patients. In: Cassem NH, Stern TA, Rosenbaum JF, et al, eds. *Massachusetts General Hospital Handbook of General Hospital Psychiatry*. 4th ed. St. Louis, Mo: Mosby; 1997:101–122
—This chapter includes a section on the practical use of intravenous haloperidol that describes dosing, cardiac and electrolyte monitoring, drug interactions, and other aspects of the use of intravenous haloperidol based on a review of the literature and the authors' extensive clinical experience.
- Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry* 2001;158:1774–1782
—A clear and detailed description of QT prolongation and TdP associated

with antipsychotic medications. A section describes the physiology of the QT interval, then extensively reviews the literature that has investigated the association between typical antipsychotic medications, TdP, and sudden cardiac death. A section on atypical antipsychotics discusses the different degrees to which these newer agents appear to prolong the QT interval.

Fayek M, Kingsbury SJ, Zada J, et al. Cardiac effects of antipsychotic medications. *Psychiatr Serv* 2001;52:607-609
 -A column that discusses the effects of antipsychotics on the QT interval. The authors discuss medication-associated and nonpharmacologic causes of QT interval prolongation. In addition, they briefly review the literature regarding the association between antipsychotics and QT interval prolongation. The column ends with clinical recommendations.

Haddad PM, Anderson IM. Antipsychotic-related QTc prolongation, torsade de pointes, and sudden death. *Drugs* 2002;62:1649-1671
 -Another comprehensive review of the subject. The article describes cardioelectrical physiology, reviews the literature that has investigated an association between antipsychotics and TdP, and outlines risk factors for the development of TdP in persons receiving antipsychotics.

Harrison MO, Krishnan KR. Antipsychotic medications and sudden cardiac death. *Psychopharmacol Bull* 2002;36:91-99
 -A review of the association of antipsychotics with QT-interval prolongation, TdP, and sudden cardiac death. The authors discuss possible mechanisms for these events and review data for each class of antipsychotics. The authors then make practical recommendations on the use of antipsychotics.

Piepho RW. Cardiovascular effects of antipsychotics used in bipolar illness. *J Clin Psychiatry* 2002;63(suppl 4):20-23
 -A brief, clear discussion of such effects. The article briefly describes the cardiovascular effects of α -adrenergic blockade by antipsychotics, then extensively discusses QT interval prolongation and TdP.

Al-Khatib SM, Lapointe NM, Kramer JM, et al. What clinicians should know about the QT interval. *JAMA* 2003;289:2120-2127
 -In this review, the authors provide clinical suggestions regarding medications associated with QT interval prolongation and TdP, including antipsychotics. The authors discuss measurement of the QT interval and describe medications whose association to QT prolongation appears to be very probable (e.g., thioridazine), probable (e.g., ziprasidone), or possible (e.g., haloperidol). The authors recommend close monitoring of the QT interval and levels of potassium and magnesium in patients receiving medications associated with QT prolongation.

Original Articles

Mehtonen OP, Aranko K, Malkonen L, et al. A survey of sudden death associated with the use of antipsychotic or antidepressant drugs: 49 cases in Finland. *Acta Psychiatr Scand* 1991;84:58-64
 -A retrospective study of 49 sudden deaths among patients taking antipsychotic or antidepressant drugs in Finland over a 3-year period. Of the 46 deaths associated with antipsychotics, all but 3 were associated with phenothiazines; thioridazine was involved in 61% of the cases and it was the only antipsychotic drug prescribed in 31%. In contrast, haloperidol was prescribed in only 13% of the cases and was never the only drug prescribed in any of the 46 cases.

Sharma ND, Rosman HS, Padhi ID, et al. Torsades de pointes associated with intravenous haloperidol in critically ill patients. *Am J Cardiology* 1998;81:238-240
 -This article describes the development of TdP in 8 of 268 patients in an intensive care unit. In 7 of the cases, the development of TdP was associated with doses of haloperidol greater than 35 mg in 24 hours. All of the patients with TdP had QTc intervals greater than 500 ms, and all but 1 had QTc greater than 550 ms. The mean maximum QTc among patients with TdP was 606 ms, while patients who did not have TdP had a mean maximum QTc interval of 493 ms. This article confirms the association between QTc prolongation and the development of TdP in patients receiving IV haloperidol and verifies the need for QTc monitoring with IV haloperidol, especially when high doses are administered.

U.S. Food and Drug Administration. Center for Drug Evaluation and Research, Psychopharmacological Drugs Advisory Committee. Meeting Transcript (for the approval of Zeldox [ziprasidone]), July 19, 2000. Available at: <http://www.fda.gov/ohrms/docket/ac/00/transcripts/3619t1a.pdf>, [3619t1b.pdf](http://www.fda.gov/ohrms/docket/ac/00/transcripts/3619t1b.pdf), and [3619t1c.pdf](http://www.fda.gov/ohrms/docket/ac/00/transcripts/3619t1c.pdf)
 -This meeting transcript describes Study 054, which compared the effect of ziprasidone on the QTc with that of other antipsychotics. In this study, 154 healthy subjects were given an antipsychotic medication (thioridazine, haloperidol, quetiapine, olanzapine, risperidone, or ziprasidone), titrated to the highest tolerated dose. The investigators found that thioridazine resulted in both the greatest mean QTc prolongation and the greatest percentage of persons with a QTc increase of greater than 60 ms. Ziprasidone caused the next greatest QTc increase among the agents studied; haloperidol caused the smallest QTc increase. Though this study provides useful data, it is not clear that these data can be directly extrapolated to the administration of antipsychotics by the intravenous route to medically ill patients.

Hoehns JD, Stanford RH, Geraets DR, et al. Torsades de pointes associated with chlorpromazine: case report and review of associated ventricular arrhythmias. *Pharmacotherapy* 2001;21:871-873
 -A case report of TdP associated with the use of chlorpromazine. The authors describe the case and present the results of a review of the Food and Drug Administration's Adverse Event Reporting System database over a 3-year period. The authors found that 12 cases of ventricular arrhythmia associated with chlorpromazine were documented, 5 of which had characteristic features of TdP.

Roe CM, Odell KW, Henderson RR. Concomitant use of antipsychotics and drugs that prolong the QT interval. *J Clin Psychopharmacol* 2003;23:197-200
 -In this study, approximately 2900 patients being treated with antipsychotics were divided into 2 groups: those receiving antipsychotics associated with possible QT prolongation and those receiving antipsychotics not associated with QT prolongation (as delineated by the International Registry for Drug-Induced Arrhythmias). The authors found that both groups of patients had similar rates of concomitant use of non-psychotropic medications that may increase the QT interval. More than half of the patients in the QT prolongation group received another medication associated with QT prolongation at some point during the 3- to 12-month follow-up period (most frequently antidepressants or antibiotics). The authors concluded that the use of other QT-prolonging drugs was not being reduced in patients taking antipsychotics that are associated with QT prolongation.