Prolonged QT Risk Assessment in Antipsychotic Overdose Using the QT Nomogram

Ingrid Berling, BMed*; Geoffrey K. Isbister, MD, MBBS

*Corresponding Author. E-mail: ingrid.berling@gmail.com, Twitter: @IBerling.

Study objective: Antipsychotic drugs are frequently reported to cause QT prolongation and torsade de pointes. We aim to investigate the potential risk of torsade de pointes in antipsychotic overdose by assessing the QT interval with the QT nomogram.

Methods: All presentations to a toxicology service between January 1987 and May 2013 were reviewed. Admissions with single ingestions of an antipsychotic greater than maximum daily dose were extracted. Demographics, dose, ECG, and outcomes (arrhythmias and death) were obtained. QT intervals in multiple leads were manually measured and the median taken. QT–heart rate (QT-HR) pairs were plotted on the QT nomogram and defined as prolonged if above the abnormal line. The QTcF (Fridericia's HR correction) was calculated and compared with dose.

Results: From 2,356 antipsychotic overdoses, 494 were included. There were no abnormal QT-HR pairs in 4 aripiprazole, 31 pericyazine, 14 trifluoperazine, and 7 haloperidol overdoses. Abnormal QT intervals occurred in 9 of 16 amisulpride overdoses (56%; 95% confidence interval [CI] 31% to 79%), 16 of 57 thioridazine overdoses (28%; 95% CI 17% to 42%), and 5 of 29 chlorpromazine overdoses (17%; 95% CI 7% to 36%). Abnormal QT intervals occurred in 5 of 41 risperidone overdoses (12%; 95% CI 5% to 27%), 10 of 202 quetiapine overdoses (5%; 95% CI 3% to 9%), and 2 of 76 olanzapine overdoses (3%; 95% CI 0.5% to 10%), but there was no correlation between dose and QTcF, and most abnormal QT intervals were at fast HR. An additional 186 single antipsychotic ingestions with noncardiotoxic coingestants had similar proportions of abnormal QT. There was 1 case of torsade de pointes in a thioridazine overdose.

Conclusion: There appeared to be significant risk of QT prolongation with amisulpride and thioridazine overdoses. Although there were abnormal QT intervals for quetiapine, olanzapine, and risperidone overdoses, they were associated with tachycardia and not dose dependent, and so were unlikely to be associated with increased torsade de pointes risk. [Ann Emerg Med. 2015;66:154-164.]

Please see page 155 for the Editor's Capsule Summary of this article.

A **feedback** survey is available with each research article published on the Web at www.annemergmed.com.
A **podcast** for this article is available at www.annemergmed.com.

0196-0644/$-see front matter

http://dx.doi.org/10.1016/j.annemergmed.2014.12.005

INTRODUCTION

Background

Cardiac arrhythmia is an important complication of drug overdose. The most common ECG abnormality is now QT prolongation, which is due to cardiac potassium channel blockade, usually the delayed rectifier potassium channel. QT prolongation is associated with an increased arrhythmogenic risk, in particular, torsade de pointes. Although rare, torsade de pointes is reported to be fatal in about 20% of cases.

Antipsychotics have been associated with QT prolongation and torsade de pointes. The increased use of antipsychotics is thought to be a cause of the increased rates of sudden death in patients treated with these medications, likely because of cardiovascular causes such as arrhythmia.[1-5] Higher rates of sudden death with therapeutic use[6] and cardiac toxicity in overdose[2] have been demonstrated for one of the older antipsychotics, thioridazine. This has resulted in the removal of thioridazine from the market.

There is considerable variation between antipsychotic drugs, including their binding to different receptors (eg, delayed rectifier potassium channel).[7] Receptor binding profiles influence the adverse effect profile (sedation, extrapyramidal signs, and anticholinergic effects) and their propensity for cardiac toxicity. With QT abnormalities being an increasing issue for drug use and development,[8] there has been particular focus on antipsychotic drugs and the QT interval.[4] QT prolongation is unlikely to be a class

Editor's Capsule Summary

What is already known on this topic

Prolongation of QT and, rarely, torsade de pointes occurs with some antipsychotic medications.

What question this study addressed

Which antipsychotic medications are associated with prolongation of the QT interval when ingested in an overdose attempt?

What this study adds to our knowledge

Thioridazine and amisulpride were more likely to produce prolonged QT at heart rates less than 105 beats/min. Abnormal QT intervals also occurred with risperidone, quetiapine, and olanzapine, but most of these patients had heart rates above 105 beats/min.

How this is relevant to clinical practice

Emergency physicians should be alert for prolonged QT for selected antipsychotic medications.

effect, so identifying individual drug-risk profiles for QT prolongation and torsade de pointes is therefore necessary.

Animal models of the effects of antipsychotic drugs on the delayed rectifier potassium channel do not always translate into clinical toxicity in humans. For instance, in vitro studies in feline cardiac tissue have shown that haloperidol and risperidone have high potency for delayed rectifier potassium channels.[9] However, human studies show that haloperidol has a clear association with QT prolongation and torsade de pointes,[10] but clinical cases of risperidone causing torsade de pointes in humans have not been reported[11] and QT prolongation is rare.[12]

Importance

Because of their underlying condition, patients treated with antipsychotic medications are at increased risk of suicide and deliberate self-harm; it is not surprising that antipsychotics are one of the most common drugs used in overdose. Evidence from human studies on the frequency of QT prolongation and torsade de pointes in drug overdose is therefore essential to guide risk assessment.

Goals of This Investigation

This study reports the potential risk of torsade de pointes in typical and atypical antipsychotic overdose by assessing the QT interval after overdose of these agents and describing the frequency of QT prolongation and of torsade de pointes with each agent.

MATERIALS AND METHODS

Study Design and Setting

This study is a retrospective review of all antipsychotic overdose presentations to a primary toxicology referral center for more than half a million people. All poisoning cases for the region are referred to the one center. A clinical database that prospectively records information on all patients admitted to the toxicology unit was reviewed to identify admissions qualifying for analysis. The database is maintained by trained personnel blinded to any study hypotheses, and clinical information for all toxicology presentations is collected prospectively on a clinical data sheet at presentation by emergency department (ED) staff. Each patient is admitted to the toxicology unit and reviewed by a clinical toxicologist, and a repeated history is collected. The database and patient records are reviewed weekly by a clinical toxicologist. Exemption for use of the database and medical records as an audit has been previously approved by the Hunter New England Area Human Research Ethics Committee.

Selection of Participants

All presentations to the toxicology service between January 1987 and May 2013 were reviewed in the database, and any overdose admission that included one of the antipsychotic drugs amisulpride, aripiprazole, chlorpromazine, clozapine, droperidol, fluphenazine, haloperidol, olanzapine, paliperidone, pericyazine, pimozide, quetiapine, risperidone, thioridazine, trifluoperazine, ziprasidone, or zuclopenthixol was extracted. The drug ingestion was confirmed from patient history taken at least twice, as well as collateral history from family, ambulance services, general practitioners, and empty medication packets. Admissions were included only if the reported ingestion involved more than the maximum daily dose according to the Australian Therapeutic Guidelines.[13] In addition, cases of antipsychotic ingestion in combination with drugs known to not prolong the QT interval (paracetamol, codeine, nonsteroidal anti-inflammatory drugs, benzodiazepines, and ethanol) were reviewed separately. Cases were excluded if any patient ingested any other potentially cardiotoxic medication in overdose, the medical record was unobtainable, the ECG could not be interpreted, the dose was below the maximum recommended daily dose, or there were fewer than 3 cases (Figure 1).

Methods of Measurement

The following data were extracted from the clinical database and patient records: demographic information (age and sex), details of ingestion (time of ingestion, time of presentation, and estimated ingested dose in milligrams),