

QT Prolongation With Migraine Medications

Case History Submitted by Randolph W. Evans, MD

Expert Opinion by Adan Ramirez Atriham, MD

Department of Family Medicine, Baylor College of Medicine

Nadim Nasir, Jr, MD, FACC

Division of Cardiology, Baylor College of Medicine and the Texas Arrhythmia Institute

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Abbreviations: LQTS long QT syndrome, DI-LQTS drug-induced long QT syndrome

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In recent years, there has been increasing concern about the risk of torsades de pointes due to medications used for migraine.

CLINICAL HISTORY

A 45-year-old woman reported a history of severe migraine without aura since she was a teenager. She presented to the emergency department with a typical severe migraine with nausea and vomiting, present for 12 hours, and unresponsive to an oral triptan. Her past medical history was otherwise negative, and she was not taking other medications.

Questions.—Before administering intravenous prochlorperazine 5 mg, promethazine 25 mg, or droperidol 2.5 mg, should she have a baseline electrocardiogram (ECG)? What is the risk of these neuroleptic agents for causing torsades de pointes? Is metoclopramide also associated with a similar risk?

EXPERT COMMENTARY

At least 300 000 cases of sudden death occur every year in the United States. Though the vast majority of these deaths occur in patients with structural organic heart disease, approximately 5% are due to ventric-

ular arrhythmias associated with the prolonged QT syndrome.¹ This syndrome can be the result of either acquired or genetically coded defects or be acquired, underlying organic heart disease, or the effect of individual medications or interactions among drugs.

Long QT syndromes (LQTS) are characterized by abnormalities in ventricular repolarization, clinically manifested by an increased incidence of syncopal episodes or even by sudden death secondary to polymorphic ventricular tachycardia (PVT). Torsades de pointes is one such form of lethal arrhythmia, originally described by Dessertenne as a PVT in which the QRS vector rotates about an isoelectric axis. Since it reminded the author of the ballet movement, it was described as a “torsades de pointes” or “twisting about the point.”² Abnormalities in potassium channel proteins play an important role during the action potential of cardiac impulse formation. In a similar fashion, drug-induced long QT syndrome (DI-LQTS) can be caused by an artificial blockage of the same potassium channels, resulting in prolongation of ventricular repolarization.³ Clinically, this may become manifest on the surface ECG as a prolongation of the corrected QT interval (usually 450 msec or greater).

Unfortunately, the variation in phenotypic expression in genetically susceptible individuals complicates use of drugs known or suspected to cause QT prolongation; this is further complicated by drug/drug interactions. Many drugs are associated with

Address correspondence to Dr. Randolph W. Evans, Suite 1370, 1200 Binz, Houston, TX 77004 or Dr. Nadim Nasir, Jr, Suite 620, 6560 Fannin, Houston, TX 77030.

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DI-LQTS, either alone or in combination with other drugs. Information about individual drugs is available through Food and Drug Administration (FDA) mandated warnings in package inserts and Internet-based databases. Commonly prescribed drugs, from antihistamines and antibiotics to chemotherapeutic agents, have been implicated. Many popular antidepressants, anticonvulsants, and neuroleptics also are included. The prevalence of LQTS is difficult to estimate, but based on the currently increasing frequency of diagnosis, it may occur in 1 in 3000 to 5000 individuals.⁴ Though these rates are low, it remains difficult to predict who may be at risk of DI-LQTS, which can occur even at therapeutic doses of the offending medication.

What, then, is an appropriate level of concern when one employs such medications? Is it cost-effective for patients to have these medications started in the hospital on a telemetry bed? What is the time course for the development of QT prolongation after initiation of these agents? Should all patients have baseline and follow-up ECGs? Do they need periodic reassessment during steady-state therapy or up-titration of the drug? All important questions to be sure, but scant information is available to guide the practitioner.

We recommend the following approach to the initiation of treatment with drugs possessing the potential for QT prolongation: (1) a careful history to screen for sudden death in family members (a history of unexplained syncope or seizures in some family members should raise a red flag to evaluate for LQTS); (2) exclusion of patients of any age with a history of multiple unexplained syncopal episodes; (3) QT monitoring before and during therapy for patients with underlying structural heart disease who already are taking a variety of cardioactive medications (particularly antiarrhythmic medications); (4) exclusion of patients taking diuretics that can predispose them to developing electrolyte abnormalities (mainly hypokalemia, hypomagnesemia, and hypocalcemia); (5) exclusion of patients with altered ability for drug clearance due to renal or liver disease; and (6) potential exclusion of patients on multiple medications. Though not all inclu-

sive, these patients will be at higher risk for developing DI-LQTS.

We recommend careful adherence to FDA black box warnings regarding use of these medications. We recommend a pretreatment ECG, evaluation of the corrected QT interval, and a repeat ECG after achieving steady-state levels. Similarly, ECGs should be obtained before and after titration or addition of medications. Any individual with unexplained syncope or seizure while on a potentially offending medication should be quickly screened for abnormalities of QT prolongation and appropriate action taken. Review of available databases on the most recent reports of drug-related QT prolongation can be helpful to the practitioner and may reduce risk.

Though some argue that DI-LQTS is not a significant epidemic, the catastrophic consequences to the patient who develops PVT and either dies or is seriously injured because of this complication is real.

This patient has no history of significant risk factors for QT prolongation besides the intake of an oral triptan for acute migraine. There is no mention of syncope or family history of syncope, sudden death, or cardiac arrhythmias. Even so, droperidol, metoclopramide, prochlorperazine, and promethazine either have been implicated in cases of DI-LQTS or have been reported to prolong the QT interval. Since all of these medications can induce PVT in a susceptible patient, a screening ECG is warranted. Unfortunately, specific quantification of an individual's risk is impossible.

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