Call “the Cleaners”
How to Treat Drug-Induced Torsades de Pointes*

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Drug-induced torsades de pointes (TDP) is the epitome of a therapeutic intervention gone awry despite the best intentions. Clinically indicated drug therapy, often involving medications that have no cardiac indications and are therefore assumed to be free of cardiac effects, unintentionally provoke QT interval prolongation and iatrogenic arrhythmias (1). Although more than 1 mechanism contributes to drug-induced long QT syndrome (LQTS) (2–4), the main factor is the incidental blockade of the IKr potassium channel at the myocardial cell membrane, leading to lengthening of the action potential (and thus QT interval prolongation) and eventually provoking early afterdepolarizations (EADs) that trigger TdP, which may deteriorate to ventricular fibrillation (1). Among hospitalized patients, current use of QT interval-prolonging medications doubles the risk of in-hospital cardiac arrest (5).

In an analogy to “the cleaners” who are called on to “fix the mess” done by others, cardiologists are called on to treat drug-induced TdP. Surprisingly, contemporary textbooks dedicate only a few lines to the treatment of TdP (6). Recommendations include the following: 1) discontinuation of the culprit drug; 2) administration of intravenous magnesium; and/or 3) intravenous isoproterenol or temporary cardiac pacing. Because TdP may present as an arrhythmic storm, it is timely to review the rationale behind these recommendations.

Discontinuation of the culprit drug, although an obvious first step, is essentially a “virtual step” at first. When drug-induced QT interval prolongation is of sufficient magnitude to cause TdP, the effects of the culprit drug on the QT interval may persist for days. This enduring QT interval prolongation, outlasting the expected half-life of the drug, takes place when torsadogenic drugs not only block IKr channels but also disrupt trafficking of newly created IKr protein toward the cell membrane (4). Every medication on board is a potential “accessory to the crime,” either through additional unsuspected IKr blocking (or even IKs blocking) or through metabolic interactions with the culprit drug. Consequently, all medications, except those absolutely essential, should be immediately discontinued. Hypokalemia aggravates the proarrhythmic effects of QT interval prolongation, and sufficient potassium supplementation to raise the potassium serum levels to high-normal levels should be given without delay (7).

Intravenous magnesium was first used for TdP “almost by accident” 3 decades ago (8). Tzivoni was studying the effects of magnesium on arrhythmias related to digitalis toxicity when a patient with TdP happened to arrive. He was given intravenous magnesium, and the response seemed miraculous (D. Tzivoni, personal communication, May 2015). This led to a prospective study of 12 patients who were treated with magnesium sulfate (injected as a slow bolus of 2 g magnesium over 1 to 2 min, “often followed” by a continuous infusion of 3 to 20 mg/min): 9 patients responded immediately, and the remaining 3 responded to a second magnesium bolus (9). As noted in the original report (9), magnesium suppresses TdP without shortening the QT interval, presumably by suppressing the EADs that trigger TdP (10). EAD suppression by magnesium has been attributed to its calcium channel-blocking effects (11) but may also be mediated by a reduction of the late
component of the sodium current (I_{Na-L}) (C. Antzelevitch, unpublished observation). Verapamil, a stronger calcium channel blocker, may be effective for TdP. Limited evidence suggests exactly that (12-15), but larger studies are necessary because verapamil is also an I_{Kr} channel blocker that could prove to be proarrhythmic.

In 1983, Kay et al. (16) made the observation that drug-induced TdP begins after sudden slowing of the heart rate, usually in the form of postextrasystolic pauses. This observation led to the use of intravenous isoproterenol or temporary cardiac pacing to prevent pause-dependent TdP, a therapeutic measure that is very effective, at least temporarily. Close attention to the mode of onset of recurrent arrhythmias is mandatory because tachycardia-mediated TdP may occur with excessive doses of isoproterenol or too rapid pacing. The balance between the antiarrhythmic and proarrhythmic effects of isoproterenol (through pause prevention vs. EAD promotion through increased calcium inflow) is a matter of the right dosage. In fact, once the pauses leading to TdP are prevented by cardiac pacing, beta-blockers may be used instead of isoproterenol.

The next line of therapy involves sodium channel (I_{Na}) blockade. Flecainide, a strong I_{Na} blocker, significantly shortens the QT interval when excessive I_{Na} inflow is the underlying etiology, as in a rare form of congenital LQTS (17). However, flecainide is contraindicated in drug-induced TdP because flecainide also blocks I_{Kr}. One textbook (6) also states that lidocaine, mexiletine, and phenytoin “can be tried” for drug-induced TdP, but the literature supporting phenytoin is unconvincing (18). Lidocaine is often the first medication injected during emergency therapy of TdP, among other reasons, because, too often, the underlying long QT remains undiagnosed (19). Although TdP often responds to a lidocaine bolus, arrhythmias tend to recur despite continuous infusions.

Mexiletine is an attractive therapy for TdP because it selectively blocks I_{Na-L} (the late component of the sodium current) (20). Of note, I_{Na-L} is an important determinant of the rate adaptation of the QT interval (21), so critical in pause-dependent TdP. Mexiletine antagonizes the prolongation in the action potential and the EADs induced by the I_{Kr} blocker sotalol (22) and is highly effective for preventing TdP in the dog model of drug-induced LQTS (23).

In this issue of JACC: Clinical Electrophysiology, Badri et al. (24) report their favorable experience with mexiletine in a clinical series of drug-induced TdP. Twelve patients with TdP refractory to conventional therapy responded to oral mexiletine with marked shortening of their QT and T_{peak-Tend} intervals. Moreover, mexiletine blunted the bradycardia-dependent QT interval prolongation and was invariably successful in preventing a recurrence of TdP (24). The limitations of the study should be noted: 1) This is a retrospective case collection (with potential sampling bias); 2) arrhythmias taking place within 2 h of the first mexiletine dose were ignored when defining arrhythmia suppression; by then, other interventions (such as correction of hypokalemia) may have contributed to the success credited to mexiletine. Nevertheless, viewed in the context of the experimental studies favoring mexiletine for drug-induced TdP (22,23), the present study supports the use of mexiletine for drug-induced TdP, particularly in view of its safety profile. The present study is one more reason for continuing our struggle against the disappearance of valuable antiarrhythmic drugs from the market once they go out of fashion (25-27). Finally, ranolazine and the new agent GS-6615, more selective I_{Na-L} inhibitors, hold promise for the therapy of acquired and congenital LQTS (28).

**REFERENCES**


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