Are there identifiable risk factors in torsade de pointes due to noncardiac drugs?

The answer is “yes, there are.”

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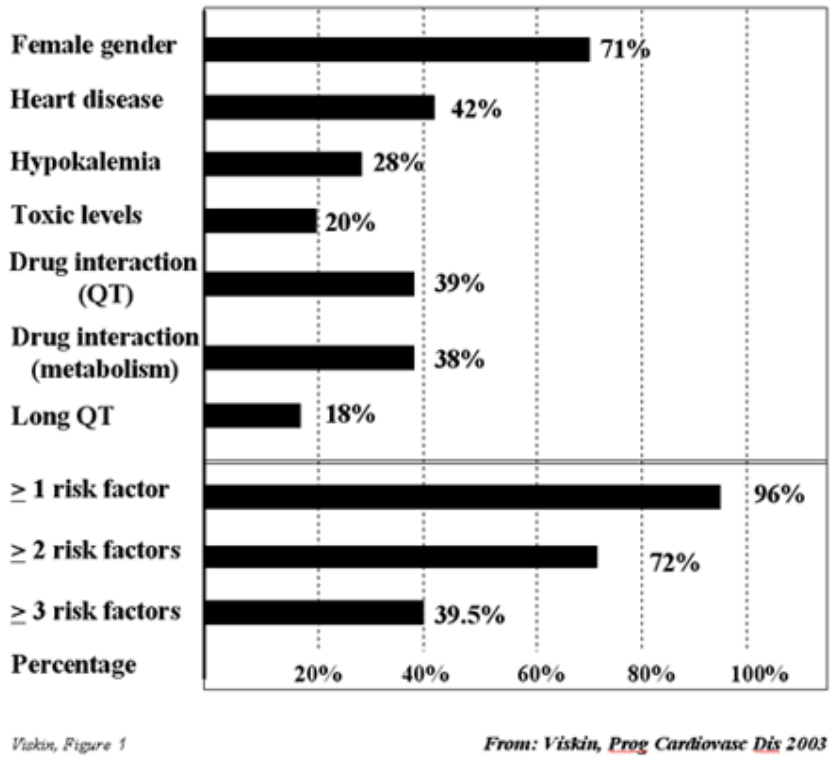
Physicians prescribing non-cardiac drugs with QT prolonging potential face a challenging dilemma: On one side, the odds of provoking torsade de pointes with a non-cardiac medication are, in general, very small, significantly less than with antiarrhythmic medications. On the other hand, long QT-related arrhythmias may suddenly and unexpectedly lead to sudden death. Moreover, because of the rarity of this complication, physicians may not even warn patients receiving *non-cardiac drugs* (that have QT-prolonging capabilities) of this potentially lethal complication, making the ultimate results even more tragic. Keeping the patient "under observation" (as recommended for patients receiving *cardiac medications* that prolong the QT interval) is likely to be futile for patients receiving *non-cardiac* drugs. This is because, in contrasts to drug-induced torsade caused by *cardiac drugs*, which often occurs during the first 72 hours of drug therapy, torsade de pointes related to *non-cardiac drugs* tends to occur much later. We recently performed a very thorough search of the literature and found published reports detailing the course of 249 patients who experienced torsade de pointes from *non-cardiac drugs* (1). Of the 162 cases of torsade de pointes that followed oral administration of a non-cardiac drug, the exact timing of the complication was reported in 114 reports. Only 18% of these patients developed arrhythmias within 72 hours from the onset of oral therapy; 42% of arrhythmias occurred between 3 and 30 days, and 40% occurred more than one month after the onset of oral therapy. Thus, to reduce the risk of torsade de pointes from a non-cardiac drug to a minimum, one most rely on the identification (and avoidance) of risk factors. Fortunately, such risk factors do exist.

To my knowledge, Dan Roden was the first to emphasize the importance of concomitant risk factors for precipitating torsade de pointes by a *cardiac drug* (2). These risk factors are shown in Table 1. Some of these risk factors are easy to identified. Thus, we recently reviewed all published reports of torsade de pointes caused by non-cardiac drugs to determine how many of these patients had easily identifiable risk factors. The list of "easily identifiable risk factors" included the following: 1) Female gender. 2) Heart disease, defined as myocardial infarction, heart failure, valvulopathy or cardiomyopathy. 3) Hypokalemia, defined as potassium serum levels <3.5 meq/L. 4) Drug toxicity *not* due to suicidal attempts, defined as the administration of doses above recommended dosages or administration of standard doses to patients with

impaired drug metabolism due to kidney or liver failure (depending on the specific drug's metabolic route). 5) Drug interactions, defined as the administration of ≥2 or more drugs that prolong the QT interval or compete for the same metabolic pathway. Drugs were considered to interfere with the metabolism of a QT prolonging drug based on data published at http://medicine.iupui.edu/flockhart/ 6) A history of familial long QT syndrome, a previous history of drug-induced torsade or a prolonged QT interval (QTc ≥450 msec) in the baseline electrocardiogram. The results of this literature analysis have been published in *Medicine (1)* and are shown in Table 2 and figure 1. In brief, we found that 96% had at least one easily identified risk factor. In fact, 72% of cases of torsade de pointes from non-cardiac drugs had at least 2 risk factors.

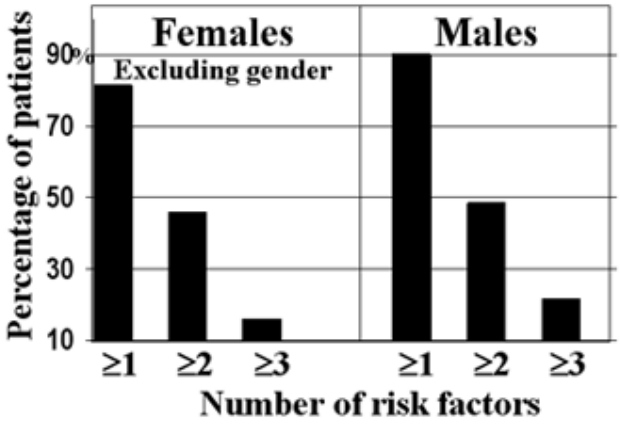
Figure 1



Risk factors for torsade de pointes from non-cardiac drugs that prolong the QT interval. *Female gender* was the most commonly identified risk factor in all drug groups: 71% of all patients with torsade de pointes were females. This observation is consistent with previous reports: Females (after puberty) have a longer QTc interval than males (3), have more pronounced QT prolongation when challenged with

potassium channel blockers (4) and are at higher risk for developing torsade de pointes when treated with antiarrhythmic drugs (5) or during spontaneous bradyarrhythmias (6). It should be noted, however, that most female patients with torsade de pointes from non-cardiac drugs had additional risk factors. In fact, other risk factors were present as commonly among females as in males [Figure 2].

Figure2



From: Zeltser, Viskin: Medicine 2003;82:282

Low potassium serum levels impair myocardial potassium outflow currents (7) and even mild hypokalemia is a major risk factor for torsade de pointes during antiarrhythmic therapy or bradyarrhythmias (2). We observed hypokalemia in 28% of patients but the cause-and-effect connection between low potassium and torsade de pointes from non-cardiac drugs is far from clear. In contrast to patients with torsade from *antiarrhythmic* medications, who regularly have straightforward reasons for hypokalemia (they often have heart disease and receive diuretics), it is not easy to explain hypokalemia in patients with torsade from *non-cardiac* drugs not treated with diuretics. Since the potassium levels "at the time of torsade" often represent the results of blood tests performed immediately after the resuscitation efforts, it is possible that the stress -- or the therapy -- that followed the arrhythmias actually led to hypokalemia instead of the other way around (8).

Patients with heart failure and left ventricular hypertrophy have down-regulation of potassium channels and up-regulation of calcium channels (9, 10), leading to action potential prolongation. Also, left ventricular

dilatation is accompanied by down-regulation of the gap-junction protein connexin43 (11). All these factors significantly increase the duration -- and the dispersion -- of repolarization and predispose a given patient for torsade de pointes when challenged with a drug that further impairs repolarization. This applies to non-cardiac drugs that incidentally block myocardial potassium channels. Heart disease was somewhat less prevalent among patients developing torsade from antihistamine therapy (as compared to other drug categories), probably representing the younger age of patients treated for allergies.

Potential drug interactions, which were present in 33%-51% of cases, have long been recognized as an important risk factor for torsade de pointes from non-cardiac drugs (12). Unfortunately, warnings on this regard included in drug labels by the manufacturers have had very little impact on physicians' prescription patterns (12). Indeed, the number of medications that may lead to adverse interactions continuously increases and it is unrealistic to expect physicians to remember all the potential adverse interactions of the drugs they prescribe without the aid of computer-generated warnings at the time drugs are prescribed or dispensed. Internet sites that continuously update the list of drugs that may cause torsade de pointes (http://www.torsades.org/) or the drugs that may lead to adverse interactions (http://medicine.iupui.edu/flockhart/) can be easily accessed.

Clinical implications. Our data cannot be used to calculate the risk of torsade among patients who have one or more risk factors because only patients with documented torsade were included in our series (1). Nevertheless, our findings suggest that the probability for developing this potentially lethal complication, which is low in the first place, may be further reduced by carefully obtaining a medical history. Patients who, according to the medical history, have no risk factors can be classified as "very low risk" patients [Table 3]. The majority of patients in need for non-cardiac medications that prolong the QT interval will fall into this category. For these patients, it is neither realistic nor sensible to require electrocardiographic screening. In this regard, several points are worth emphasizing: 1) numerous methodological problems make estimation of the rate-corrected QT problematic (13, 14). 2) Data on the value of the electrocardiogram for accurately identifying those patients who are likely to develop torsade are limited. 3) Our data suggest that only cardiac electrophysiologists with

expertise on cardiac arrhythmias can reliably calculate the QTc. The majority of physicians in other disciplines of medicine are likely to err when estimating the QTc (15). Consequently, requiring electrocardiographic evaluation of "very low risk patients" prior to the onset of therapy with non-cardiac medications that may prolong the QT is not only impractical, but will also lead to QTc estimates that will either be too long or too short in many cases. 4) Even a completely normal QT is not fail-proof, as exemplified by an elderly woman who carried a LQTS mutation but had a completely normal QTc yet developed torsade de pointes when treated with cisapride (16). Although female gender is an important risk factor for drug-induced torsade, we found (1) that females who actually develop arrhythmias generally have (in 83% of cases) additional "easily identifiable risk factors." Therefore, females *without* additional risk factors are classified as "low risk patients" (Table 3). In view of the limitations of electrocardiogram interpretation mentioned above, electrocardiographic screening of all female patients prior to the onset of therapy is not essential. On the same note, the chances of finding hypokalemia in non-cardiac patients not receiving diuretics are so low that making routine evaluation of potassium serum levels for these patients seems superfluous.

The most important preventive measure for low-risk patients is to carefully avoid *drug interactions*. Concomitant administration of two or more drugs is unsafe when more than one medication prolongs the ventricular repolarization or when the metabolism of a QT-prolonging drug is slowed down by a second drug, resulting in high drug levels. The importance of drug interactions in causing proarrhythmic effects is demonstrated by the "anti-reflux" drug cisapride. Among 57 patients with drug induced torsade due to cisapride reported to the Food and Drug Administration within a 3-year period (17), concomitant treatments with ketoconazole or erythromycin (two drugs that also prolong the QT interval and increase the cisapride serum levels by interfering with its hepatic metabolism) was reported in 56%. Additional QT-prolonging therapy or electrolyte imbalance existed in the rest (17). Similarly, in a prospective study of children treated with cisapride, 30% of children developed a long QT interval (18), but only 2 developed torsade de pointes: both of these children also received erythromycin (18).

Patients with *organic heart disease*, particularly those with marked left ventricular hypertrophy and heart failure, are considered to be at *medium risk* for developing torsade de pointes when treated with medications that further prolong repolarization. However, our estimations should be viewed with caution and a cautious approach is advised: 1) Alternative therapies that do not prolong the QT should be preferred for patients with heart disease whenever possible. 2) As opposed to low-risk patients, patients with heart disease generally have electrocardiograms already. These electrocardiograms should be carefully reviewed for the presence of baseline repolarization abnormalities (19). A QT interval of long duration and abnormal morphology indicate higher risk. 3) Patients with heart disease often receive diuretics. These patients should receive potassium supplementation to keep their potassium serum levels at the high normal range when therapy with any QT-prolonging medication is initiated.

Concomitant administration of two drugs that lead to QT prolongation should be avoided whenever possible, especially if additional risk factors (like female gender or the presence of organic heart disease) are present. The potential risks and benefits of such combination, and of any potentially alternative therapy, should be considered. Although combination therapy will be uneventful in most cases, it will be difficult to justify the selection of drugs with interactions if arrhythmic complications prompt legal action. If combination therapy is necessary, performance of repeated electrocardiograms is warranted. It should be recognized, however, that interpretation of these traces will be difficult for several reasons. First, patients receiving two or more drugs that prolong repolarization will inevitably have some degree of QT prolongation. Due to the overlapping between the QT intervals of patients with and without complications, the QT and QTc intervals after drug therapy are of such limited value for predicting proarrhythmia that one can only say that the longer the QT prolongation the higher the risk. Second, as mentioned above, proarrhythmia from non-cardiac drugs appears to be a relatively late complication. Accordingly, the yield of hospitalization for the purpose of electrocardiographic monitoring during initiation of non-antiarrhythmic drugs that prolong QT in high-risk patients will be low. The main role of electrocardiographic monitoring is to identify the "warning signs" that precede torsades de pointes. These warning signs include the appearance of prominent U waves, abnormal biphasic QT segments, extrasystoles

and “post-extrasystolic U wave augmentation” (20). Indeed, a recent animal study supports the notion that the height of pathologic U waves may be a better predictor of drug-induced torsade than the QT prolongation (21). Finally, every patient receiving non-cardiac drugs that have the potential of causing QT prolongation, especially those at moderate or higher risk, should be informed that a syncopal episode is an important warning sign of a possible dangerous arrhythmia. These patients should be instructed to stop the medication and immediately contact his/her physician if a passing out spell or the near equivalent occurs..

In conclusion, *there are* risk factors for torsade de pointes from non-cardiac drugs and many of them are easy to identify. The odds of running into serious, even fatal complications are small, especially if simple precautions are taken. Yet, the risk cannot be ignored, especially if safer alternative drug therapy is available. As with other rare and potentially fatal complications, like fatal allergies or blood idiosyncrasies, the long QT syndrome should be an ever reminder that no medication is completely innocuous and that the need for therapy, any therapy, should always be considered with care.

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Table 1. Factors that increase the risk for torsade de pointes among patients challenged with torsadogenic agents or bradyarrhythmias.*

Female gender
Hypokalemia, hypomagnesemia
Diuretic use**
Bradycardia (especially recent heart rate slowing)
Congestive heart failure or cardiac hypertrophy
Congenital long QT syndrome
Mitral valve prolapse ?
Acquired Immune Deficiency Syndrome ?
Baseline ECG: QT prolongation or T wave lability.
Genetic mutations or polymorphisms leading to dysfunctional myocardial channels.
Post-exposure ECG:
• Marked QT prolongation
• Pathologic TU morphology (biphasic T-waves)
• Marked post-extrasystolic QTU changes.
• High drug-levels***

*Modified from Roden(2). **Diuretics increase the risk for torsade independently of electrolyte serum levels. ***Except for quinidine.

Table 2. Distribution of patients according to the type of drug causing torsade de pointes and the risk factors identified.

Drug type	Psychiatric	Antibiotic	Antihistamine	Miscellaneous	p Value
Risk factor	**(n=70)**	**(n=69)**	**(n=38)**	**(n=72)**	
Female gender	71.4%	64.5%	71.1%	75.0%	0.96
Heart disease	43.1%	52.6%	17.1%	41.0%	0.11
Hypokalemia	17.9%	30.6%	17.6%	42.6%	0.17
Drug interactions	44.7%	31.5%	51.4%	33.3%	0.28
Excessive dose	27.0%	8.7%	28.9%	11.0%	0.32
Long QT	17.1%	15.9%	26.3%	18.1%	0.77
Risk factors	2.2 ± 1.0	2.0 ± 1.2	2.5 ± 0.9	2.1 ± 1.1	0.10

Drug interactions = Treatment with a medication that impairs the metabolism of a QT-prolonging drug or concomitant use of ≥2 QT-prolonging medications concomitantly. **Long QT** = a familial history of long QT syndrome, a history of torsade de pointes triggered by a different drug in the past or an obviously prolonged QT interval prior to drug administration. **Risk factors** = mean (± standard deviation) number of risk factors per patient. From Zeltser et. al.(1)

Table 3. Prevention of torsade de pointes with non-cardiac medications that prolong the QT interval.*

Risk	nition	Screening ECG	Follow-up ECG	Cardiologist consultation	ECG monitoring
Very Low	isk factors (Table 3) are present	Not required	Not required	Not required	Not required
Low	ales without risk factors	Not required	Not required	Not required	Not required
Medium	rt disease	Advisable	Advisable	Advisable	Not required
High	g interactions†	Required	Required	Advisable	Questionable
Very high	History of LQTS‡	Mandatory	Mandatory	Mandatory	Mandatory

*The recommendations presented in this manuscript and summarized in this table reflect the authors' views. There are no controlled trials to support these recommendations. †Administration of more than one drug that can cause QT prolongation or that may compete for a metabolic pathway should be avoided. If this is not possible, careful monitoring of the pre- and post-treatment electrocardiogram and repeated assessment of the potassium serum levels are warranted. However, the value of continuous electrocardiographic monitoring is questionable (see text). ‡Administration of drugs that may prolong QT is practically contraindicated for patients with baseline long QT or who have experienced torsade de pointes when treated with other drugs. *Adapted from Viskin: Long QT syndrome from non-cardiac drugs.(22)*