Assessing Risk of QTC Prolongation

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Monitoring patients for possible QTC prolongation with psychotropic use can be difficult--even more so in children or adolescents. What screening and treatment techniques should be used for maximum therapeutic benefit with minimum cardiac risk?

Certain psychotropic medications and somatic medications can increase the risk of lethal *torsade de pointes* through a mechanism of blocking cardiac conduction channels (e.g., Na\(^+\), K\(^+\) and/or Ca\(^{++}\)). The best available parameter for assessing risk of *torsade de pointes* is measuring the rate-corrected QT interval (QT\(_c\)) on electrocardiogram (Labellarte et al., 2003a; Tisdale et al., 2001).

While it is necessary to identify whether or not a psychotropic medication can prolong QT\(_c\) alone or in combination with other medications, the list of marketed medications that are known to prolong QT\(_c\) is incomplete (Labellarte et al., 2003a). Available QT\(_c\) safety data are a hodgepodge of post-marketing clinician case reports, animal and human myocyte conduction studies using proprietary technology, and treatment studies screening for QT\(_c\) prolongation. Of the medications known to prolong QT\(_c\), some are more dangerous than others at clinical doses, in overdose or in combination with other medications.

Few of the studies reporting cardiac safety of psychotropic medications have involved children and adolescents. Three practical guidelines discuss conservative screening and monitoring of children and adolescents who require treatment with psychotropics known or suspected to cause QT\(_c\) prolongation (Labellarte et al., 2003a) (Table).

**Medications That Prolong QT\(_c\)**

The most comprehensive and easily accessed reference source for somatic and psychotropic medications known or suspected to cause QT\(_c\) prolongation is at <www.Qtdrugs.org>. This Web site is maintained by the University of Arizona Center for Education and Research on Therapeutics in Tucson, Ariz. It lists cautious medication combinations by identifying which medications could cause additive pharmacodynamic risk when combined with psychotropics that prolong QT\(_c\).

A more concise list of psychotropics that can contribute to QT\(_c\) prolongation is inspired by earlier recommendations from the American Heart Association (Gutgesell et al., 1999). The list contains no surprises: older medications (e.g., tricyclic antidepressants, phenothiazines, butyrophenones and pimozide [Orap]) that have been known for decades to cause QT\(_c\) prolongation/*torsade de pointes*. The only newer medication on the list is ziprasidone (Geodon), which has caused a mild but measurable QT\(_c\) prolongation in a comparison study (~21 msec) (Harrigan et al., 2004) but has not caused cardiac events in clinical or research settings (Daniel, 2003). In contrast to the old-school medications, ziprasidone's potential impact on ion channels has not been studied.

The older medications have not compared well in QT\(_c\) monitoring studies of adults. Droperidol (Inapsine) caused the highest documented QT\(_c\) prolongation (~59 msec) (Lischke et al., 1994) and also has the highest relative risk of causing QT\(_c\) duration >450 msec (Reilly et al., 2000).

Thioridazine (Mellaril) had the next highest relative risk (Reilly et al., 2000), and also caused noteworthy QT\(_c\) prolongation (~30 msec to 36 msec) compared to haloperidol's (Haldol) minimal QT\(_c\) prolongation (8 msec) in the comparison study by Harrigan and colleagues (2004). The impact of haloperidol on QT\(_c\) duration/*torsade de pointes* has debatable clinical relevance (Di Salvo and O’Gara, 1995; Hatta et al., 2001), but haloperidol merits ECG monitoring in light of emerging data that its active metabolites may have different patterns of toxicity (Kalergutkar et al., 2003).

**Important Drug Interactions**

The most comprehensive and easily accessed reference source for pharmacokinetic interactions is maintained at <www.drug-interactions.com> by the Indiana University Department of Medicine. While the Web site does not focus specifically on interactions that contribute to QT\(_c\) prolongation, it is easy to extrapolate a working list of important medications that could cause worrisome metabolic inhibition and potentially increased risk of QT\(_c\) prolongation.
In addition, protein-binding competition can potentially cause increased serum levels of medications that prolong QTc when combined with seemingly benign medications that are highly protein-bound (e.g., aspirin, valproic acid [Depakene], herbal preparations). Unclear pharmacokinetic mechanisms also result in increased exposure to psychotropics that prolong QTc with a few identified medication combinations, e.g., pimozide plus sertraline (Zoloft) (Zoloft package insert).

**Pretreatment Risk Factors**

Pretreatment risk factors of QTc prolongation are rare but can be easily screened. Screening includes pertinent medical history for signs/symptoms of cardiac events, including syncope-like events and pertinent family history for cardiac events such as syncope-like events, sudden death or congenital deafness (which can be associated with an inherited variant of long QT syndrome) (Ocal et al., 1997). Pretreatment laboratory test screening, when appropriate, would test serum for hyponatremia, hypokalemia or hypermagnesemia.

**ECG Screening of QT**

Briefly, the QT interval represents the period of cardiac repolarization of the ventricular action potential. If the observed QT interval is too long, it suggests that cardiac repolarization is too slow and therefore unstable (Haddad and Anderson, 2002; Khan, 2002).

The range of normal QT values in children and adolescents has roughly a mean of 400 msec with a standard deviation of 25 msec to 30 msec. Therefore, a QT value that exceeds two standard deviations (>450 msec to 460 msec) is too long. A QT >450 msec is associated with increased mortality in the elderly (Labellarte et al., 2003a; Robbins et al., 2003), and QT >500 msec is associated with increased mortality at all ages (Labellarte et al., 2003a; Moss, 1993).

Similarly, any prolongation from baseline that exceeds two standard deviations is too much; an increase in QT >60 msec from baseline is also associated with increased mortality (Haddad and Anderson, 2002; Labellarte et al., 2003a).

However, measuring QT duration is a limited clinical screening tool in pediatric psychopharmacology because of variability in rate-correction formulas (Tisdale et al., 2001); variability in clinician accuracy (Labellarte et al., 2003b); variability between expert clinician readings and ECG computerized printouts (Miller et al., 2001); and normal QT variability related to fear, postural changes or time of day. Additionally, ECG measurement may not be sensitive enough to detect QT disturbance. Most important, documentation of baseline QT duration within the normal range is not a guarantee that environmental factors (including drug effects) will not cause QT prolongation.

Psychiatrists should be able to screen ECGs for changes associated with QT prolongation before and during treatment, but are not required to be experts on ECG interpretation. In addition, the computer readout of an ECG is not reliable when confounding factors are present (i.e., tachycardia, bradycardia, unusual T-wave morphology, any arrhythmia including bundle branch block or significant U-waves).

Clinical guidelines suggest consulting a cardiologist if the QT stays prolonged after discontinuing medication, if cardiovascular symptoms are present, or if pre-existing cardiac disease or strong family history is a factor (Wilens et al., 1996). Several other QT scenarios occurring during treatment also merit consultation: QT duration >480 msec; QT prolongation >60 msec over pretreatment duration, or QT duration >450 msec after 10% to 15% increase (Labellarte et al., 2003a).

A child and adolescent psychiatrist should consult a cardiologist familiar with QT measurement if they are uncertain about the clinical significance of QT status before treatment or during careful monitoring of patients on medications that can prolong QT. If the utility of medications that can prolong QT is in question, perhaps safer alternatives should be prescribed.

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References


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