Drug-Induced QT Interval Prolongation in Children: Are the Kids Alright?

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Torsades de pointes (TdP) is a polymorphic ventricular tachycardia associated with prolongation of the heart rate–corrected QT (QTc) interval on an electrocardiogram (ECG).[1] TdP can be catastrophic, as it may result in sudden cardiac death.[1] QTc interval prolongation may be inherited or acquired. The inherited form is represented by congenital long QT syndrome, of which there are at least 15 types,[2] whereas the acquired form is most commonly caused by drugs.[3] In the past 3 decades, several drugs, including astemizole, cisapride, grepafloxacin, prenylamine, and terfenadine, have been withdrawn from the Canadian market because of deaths due to TdP.[4] Nonetheless, more than 100 drugs with the potential to prolong the QTc interval and cause TdP remain available.[5]

Although most clinicians are familiar with the potential for drug-induced QTc interval prolongation and TdP in adults, many are less aware that this adverse drug reaction can also occur in pediatric populations. However, many cases of drug-induced TdP in children have been published.[6] Pediatric cases of TdP have been associated with various drugs, including astemizole, cisapride, pentamidine, risperidone, antiarrhythmic agents (amiodarone, procainamide, and sotalol), and antifungals (fluconazole and voriconazole).[6]

In the current issue of the *Canadian Journal of Hospital Pharmacy*, Morris and others[7] review the literature regarding QT interval prolongation associated with domperidone in non-oncologic pediatric patients. Domperidone is the gastrointestinal promotility agent of choice for pediatric gastroesophageal reflux disease, which typically occurs between 5 and 18 months of age.[7] These authors describe the findings of 3 prospective cohort studies, 1 randomized controlled trial, and 1 case report of domperidone use in a total of 137 children ranging in age from 2 days to 9 months.[7] For most of these patients, QTc interval prolongation did not occur, but for 6 patients the QTc interval was abnormally long (≥ 450 ms), including 3 with QTc interval above 460 ms, to a maximum of 490 ms.[8] In one of the prospective studies, domperidone was associated with significant lengthening of the mean QTc interval relative to pretreatment values in neonates.[9] Although none of the patients represented in this literature review had a QTc interval above 500 ms or experienced an increase in QTc interval of more than 60 ms relative to the pretreatment value (the generally accepted thresholds for a marked increase in risk of TdP[6]), drug-induced QTc interval prolongation to greater than 450 ms is reason for concern. Fortunately, none of the patients in this analysis experienced TdP or sudden cardiac death.

The overall incidence of drug-induced TdP is not well described for adult populations and is generally unknown for pediatric populations. The incidence of TdP associated with various drugs (determined in overwhelmingly adult populations) ranges from 2% to 12%, depending on the drug, the dose, and other risk factors.[3] In one of the reports reviewed by Morris and others,[7] the incidence of QTc interval prolongation associated with domperidone in infants was 4.4%.[10]

Drug-induced QTc interval prolongation and TdP depend heavily on risk factors and occur only rarely in patients without concomitant predisposing factors.[6] For adults, the risk factors include female sex; advanced age (> 65 years); hypokalemia, hypomagnesemia, or hypocalcemia; heart failure with reduced ejection fraction; bradycardia; treatment with more than one QTc interval–prolonging drug; and conditions leading to elevated plasma concentrations of such drugs, such as kidney or liver disease, drug interactions, and rapid IV administration.[6] It is unknown which of these risk factors (excluding older age) also apply to pediatric populations. In one small study (n = 31), independent risk factors for domperidone-associated QTc interval prolongation in neonates were advanced gestational age and, paradoxically, serum potassium concentration at the upper limit

of normal.[9] The reason for an association with high-normal serum potassium concentration, rather than the widely accepted risk factor of hypokalemia, is unclear. Given what is known about effects on potassium channels, it seems likely that, similar to the situation for adults, hypokalemia, hypomagnesemia, bradycardia, and elevated plasma concentrations of QTc interval–prolonging drugs are risk factors for pediatric patients.[6] However, female sex is not a risk factor for QTc interval prolongation and TdP in prepubertal children. Evidence shows that the QTc interval is similar in boys and girls until the onset of puberty, at which time QTc intervals diverge.[11] This divergence is likely the result of increasing testosterone production at puberty in males, which has been shown to be associated with a shorter QTc interval.[6] Therefore, female sex is a risk factor for QTc interval prolongation and TdP only at or following puberty.

Recommendations for hospitalized adult patients receiving therapy with a QTc interval–prolonging drug include continuous monitoring of the QTc interval and maintenance of serum potassium, magnesium, and calcium concentrations within the normal range.[1] If the patient's QTc interval exceeds 500 ms or increases by more than 60 ms over the pretreatment value, recommended interventions include use of alternative, non–QTc interval–prolonging therapy, where possible; assessment of potential drug interactions, bradyarrhythmias, or electrolyte abnormalities; and readiness to manage TdP should it occur.[1] Recommendations for hospitalized children or neonates receiving therapy with QTc interval–prolonging drugs have not been published, but it seems reasonable to promulgate recommendations similar to those for adults. For pediatric patients with risk factors for TdP but for whom continuous QTc interval monitoring is not feasible, a 12-lead ECG should be obtained at baseline and then 3–7 days after initiation of QTc interval–prolonging therapy.

The review by Morris and others[7] serves as a reminder that drug-induced QTc interval prolongation is not restricted to adults and that children and neonates are also susceptible, particularly if they have predisposing factors. Appropriate QTc interval monitoring and attention to modifiable risk factors are important for reducing the risk of QTc interval prolongation and TdP in children and neonates receiving therapy with QTc interval–prolonging drugs.

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