PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the University of Virginia Children's Hospital

Volume 11 Number 10 October 2005

Drug-induced QT Prolongation: Examples from the Pediatric Literature

Marcia L. Buck, Pharm.D., FCCP

Prolongation of the QT interval to more than 440 to 460 msec on electrocardiogram (ECG) has been associated with a wide variety of drugs. The use of these drugs may place patients at greater risk for ventricular arrhythmias, including torsades de pointes. Since the 1990s, identification of QT prolongation and torsades has led to the removal of several drugs from the market in the United States, including terfenadine, astemizole, thioridazine, and grepafloxacin, while many others have been required by the Food and Drug Administration (FDA) to carry additional safety labeling warning of the potential risk.[1-5]

Currently, most drugs in development undergo screening for potential QT prolongation. Unfortunately, the ability of a drug to produce torsades is more difficult to determine during clinical trials. Many drugs which prolong the QT interval do not appear to produce torsades; however, some drugs that produce only minimal effects on the QT interval have been linked to a significant number of torsades cases.[5] In addition, these trials rarely include infants and children, who may be at greater risk for arrhythmias. As a result, most reports of QT prolongation in the pediatric population have come from postmarketing surveillance and adverse drug reaction reporting systems. This issue of *Pediatric Pharmacotherapy* will review the proposed mechanism of drug-induced QT prolongation and provide recent examples from the pediatric literature.

Proposed Mechanism

Prolongation of the QT interval (or QT_c interval when corrected for heart rate) results from lengthening of ventricular action potentials. This can be caused by blockade of potassium channels which are responsible for terminating the plateau phase of the action potential. Although many potassium channels may produce this effect, it is believed that the majority of QT-prolonging drugs block the human ether-a-go-go-related gene (HERG) ion channel that conducts the rapidly activating delayed rectifier potassium current (I_{Kr}). Drug-induced torsades is much less common than QT prolongation because blockade of HERG is just one of many factors that work together to alter repolarization. The presence of other factors, such as hypokalemia, bradycardia, concomitant administration of multiple QT-prolonging drugs, or genetic predisposition, may place patients at a higher risk for serious arrhythmias. Preclinical testing for drugs in development now routinely includes assessment of their ability to block HERG and I_{Kr}.[1-5]

Cisapride

Cisapride was introduced in the United States in 1993 and quickly became a common treatment for gastroesophageal reflux (GERD). Within two years, QT prolongation and torsades had been reported in adults. In 1996, Lewin and colleagues reported the first case of cisapride-induced QT prolongation in a child.[6] A 2-month-old infant with GERD developed bradycardia during treatment with cisparide at a dose of 1.2 mg/kg/day. An ECG performed at that time revealed 2:1 atrioventricular conduction and a QT interval of 510 msec. After discontinuation of cisapride, the ECG returned to normal.

Since publication of that initial case, several other cases of cisapride-induced QT prolongation have been reported in pediatric patients. Three prospective studies have attempted to assess the potential risk associated with cisapride. In 1998, investigators from the Children's Hospital of Los Angeles performed ECG studies in 30 children prior to and after initiation of cisapride.[7] Cisapride significantly lengthened the QT interval, with a mean increase of 15.5±4.6 msec (mean±SEM). The authors also combined the results from these 30 children with an additional 71 patients who had ECG recordings only after starting therapy. In the combined population, 12 of the 101 patients (12%) had QT intervals greater than 440 msec. The authors concluded that cisapride use in children was associated with a modest increase in the QT interval, but that the incidence of significantly prolonged QT intervals was low.

Also that year, Hill and colleagues studied the effects of cisapride on ECG recordings in 35 children.[8] The mean QT interval was 428±35 msec. Eleven (31%) of the children had a QT interval greater than 450 msec. Two patients had documented torsades. Both were receiving a macrolide antibiotic which may have inhibited the metabolism of cisapride through cytochrome P450 3A4, putting these patients at increased risk for toxicity.

Ramirez-Mayans and colleagues conducted a comparison study of 63 children (mean age 29 months) who were receiving cisapride at an average dose of 0.6 mg/kg/day and 57 children (mean age 27 months) who served as controls.[9] Five children from the cisapride group (8%) and six from the control group (11%) had QT intervals greater than 460 msec. In three of the cisapride-treated patients, the QT interval returned to normal after discontinuation of the drug. When the cisapride and control groups were compared, there was no significant difference in the QT interval ($p = 0.4$). None of the children in the study experienced arrhythmias.

Because of the potential risk for arrhythmias, particularly when used with interacting drugs, Janssen stopped marketing cisapride in the United States in July 2000. It is now available only through the manufacturer's limited-access protocol. Its use is restricted to those patients unable to tolerate or resistant to standard therapies and requires intensive monitoring.[10]

Doxapram

Doxapram, a central respiratory stimulant, is occasionally used in the treatment of apnea of prematurity that is not responsive to methylxanthines. In 1998, it was first reported to cause prolongation of the QT interval in neonates.[11] In 2001, Maillard and colleagues conducted a prospective study of the effects of doxapram on the QT interval in 40 preterm infants.[12] Patients were treated with doxapram at a dose of 0.5 to 1 mg/kg/hr, with ECGs obtained prior to initiating therapy and during the first 3 days of treatment. The authors found a statistically significant lengthening of the QT interval (394±4 msec at baseline compared to 409±4 msec after treatment, $p = 0.0065$). Six of the patients (15%) had a QT interval greater than 440 msec, but no evidence of a conduction disorder. The authors recommend ECG follow-up in all neonates treated with doxapram.

Anesthetics

Several anesthetic agents, including isoflurane, sevoflurane, propofol, and thiopental, have been associated with QT prolongation. Earlier this year, Whyte and colleagues studied the effects of propofol and sevoflurane on the QT interval in 50 children (ages 1 to 16 years) undergoing elective surgery.[13] Propofol, at a concentration of 3 mcg/ml, produced an insignificant mean increase in QT interval of 8 msec in lead II and 5 msec in V5. Sevoflurane produced a much greater effect, with a mean prolongation of more than 30 msec in both leads. Using an assessment of the time interval between the peak and end of the T wave as a measure of transmural dispersion of repolarization (an indicator of the potential to produce torsades), the authors found no evidence of an increased risk for arrhythmias.

Droperidol

Droperidol has long been used in the perioperative setting to prevent anesthesia-induced nausea and vomiting. Its association with QT prolongation has been known since the early 1990s. On December 5, 2001, the FDA issued a black box warning for droperidol, calling attention to this adverse reaction. The revision of the product labeling resulted in the removal of droperidol in many institutions, with overall use of the drug declining by as much as 90%. The appropriateness of a black box warning, however, continues to be questioned by health care professionals, as the clinical significance of this reaction in the intraoperative and postoperative setting remains to be determined.[14,15]

In 2004, a retrospective analysis was conducted to assess the effect of droperidol on the QT interval in 20 children after cardiac surgery.[16] Assessments were made prior to and at 15 minute intervals after a 100 mcg/kg IV droperidol dose. Droperidol produced a significant increase in the QT interval at 15 minutes, but values returned to normal by 30 minutes. No arrhythmias were observed.

Two recent studies in adults have added further information to the ongoing debate over the safety of droperidol. White and colleagues conducted a placebo-controlled trial of low-dose droperidol (0.625 or 1.25 mg) in 60 adults undergoing otolaryngologic procedures with general anesthesia.[17] Within 3 to 6 minutes, QT intervals were prolonged, but there was no difference among the groups (15±40 msec, 22±41 msec, and 12±35 msec for the 0.625 mg dose, 1.25 mg dose, and placebo groups, respectively). The number of patients exhibiting QT prolongation greater than 10% of baseline was also no different among the groups. No arrhythmias were noted.

Charbit and colleagues conducted a comparison study of droperidol (0.75 mg IV) and ondansetron (4 mg IV) in 85 adults with postoperative nausea and vomiting.[18] Baseline ECGs were obtained, as well as follow-up studies at 1, 2, 3, 5, 10, and 15 minutes. Continuous ECG monitoring was maintained for an additional 3 hours in eight patients from each group. At baseline, the QT interval was prolonged (> 450 msec in men, >470 msec in women) in 21% of patients. Compared to baseline values, the QT interval was significantly prolonged after both antiemetics. The maximal QT prolongation with droperidol was 17±9 msec, occurring at 2 minutes after administration. Maximal prolongation with ondansetron was 20±13 msec, occurring after 3 minutes. The authors concluded that QT prolongation occurs in a similar manner with both drugs. In addition, the confounding effects of general anesthetics make it difficult to assign a greater degree of risk to droperidol than other agents in this setting.

Atypical Antipsychotics

The atypical antipsychotics are useful adjuncts in the management of children and adolescents with schizophrenia, schizo-affective disorders, bipolar disorder, Tourette's syndrome, and autism. In 2004, Kurth and Maguire reported the case of a 14-year-old who developed QT prolongation after a quetiapine overdose.[19] During a hospital stay, the patient ingested nineteen 100 mg quetiapine tablets (26 mg/kg) that he had been hoarding as a suicide attempt. An ECG obtained within an hour of the overdose revealed a QT interval of 453 msec, compared to a value of 411 msec obtained from an initial ECG performed on admission. A subsequent ECG 40 minutes later showed further lengthening to 618 msec. Six hours later, the interval had declined to 436 msec. No arrhythmias were noted.

The association between QT prolongation and ziprasidone use has also been well documented. Ziprasidone carries detailed warning information in the product labeling, based primarily on reports in adults. In the January issue of *The Journal of the American Academy of Child and Adolescent Psychiatry*, Blair and colleagues published a prospective, open-label trial to assess ECG changes in 20 children receiving ziprasidone.[20] The patients (mean age 13.2±3 years) were treated with an average ziprasidone dose of 30±13 mg/day for up to 6 months. The mean QT prolongation from baseline to peak measurement was 28±26 msec. The degree of prolongation was not related to dose. Three patients (15%) had QT intervals greater than 440 msec. Based on their results, the authors recommend ECG monitoring in children treated with ziprasidone, particularly when higher doses or concomitant QT-prolonging drugs are used.

Atomoxetine

An overdose of atomoxetine was recently reported to produce QT prolongation in a 15-year-old boy.[21] The patient ingested an intentional overdose of 1,200 mg (22 mg/kg). He experienced seizures, followed by a period of anxiety, tremulousness, and dry mouth. An ECG obtained 3 hours after ingestion revealed a QT interval of 607 msec, which declined to 435 msec at 6 hours. The patient experienced no other adverse effects.

Assessment of Risk

The literature on drug-induced QT prolongation is extensive. While this adverse reaction is listed in most dosing references, evaluating the degree of risk is difficult. The Arizona Center for Education and Research on Therapeutics maintains a website (www.qtdrugs.org or www.torsades.org) which lists over 100 drugs associated with QT prolongation, ventricular tachycardia, and torsades. Drugs are separated into those known to cause torsades, those which pose a possible risk, and those which should be avoided in patients with congenital long QT syndrome. The site also provides a list of drugs which are unlikely to cause torsades in usual recommended doses unless the patient has other underlying risk factors, such as concomitant use of other drugs which prolong QT or inhibit the target drug's metabolism. In addition, the website offers a number of educational resources and information on submitting new case reports.

In a recent supplement to *The Journal of Family Practice*, Slama published a useful algorithm for working with drugs associated with QT prolongation and torsades.[22] The author highlighted five steps to minimize risk, including identification of underlying patient risk factors, identification of all QT-prolonging drugs, consideration of alternatives, use of baseline ECGs, and recommendations for monitoring.

Summary

Prolongation of the QT interval has been associated with many drugs, including several commonly used in infants and children. Few cases of torsades have been reported in children, although clinicians should be aware of the potential for this serious adverse effect, especially in infants. Careful drug selection, including avoidance of concomitant QT-prolonging drugs or drugs which inhibit their metabolism, should help to minimize the risk of drug-induced arrhythmias.

References

1. Sanguinetti MC, Mitcheson JS. Predicting drug-hERG channel interactions that cause acquired long QT syndrome. Trend Pharmacol Sci 2005;26:119-24.
2. Finlayson K, Witchel HJ, McCulloch J, et al. Acquired QT interval prolongation and HERG: implications for drug discovery and development. Eur J Pharmacol 2004;500:129-42.
3. De Bruin ML, Pettersson M, Meyboom RHB, et al. Anti-HERG activity and the risk of drug-induced arrhythmias and sudden death. Eur Heart J 2005;26:590-7.
4. Eckhardt LL, Rajamani S, January CT. Protein trafficking abnormalities: a new mechanism in drug-induced long QT syndrome. Br J Pharmacol 2005;145:3-4.
5. Olsen KM. Pharmacologic agents associated with QT interval prolongation. J Fam Pract 2005 Jun;Suppl:S8-S14.
6. Lewin MB, Bryant RM, Fenrich AL, et al. Cisapride-induced long QT interval. J Pediatrics 1996;128:279-81.
7. Khongphatthanayothin A, Lane J, Thomas D, et al. Effects of cisapride on QT interval in children. J Pediatrics 1998;133:51-6.
8. Hill SL, Evangelista JK, Pizzi AM, et al. Proarrhythmia associated with cisapride in children. Pediatrics 1998;101:1053-6.
9. Ramirez-Mayans J, Garrido-Garcia LM, Huerta-Tecanhuey A, et al. Cisapride and QTc interval in children. Pediatrics 2000;106:1028-30.
10. Propulsid® statement. Janssen Pharmaceutica, 2005. Available at www.janssen.com (accessed 10/6/05).
10. De Villiers GS, Walele A, Van der Merwe PL, et al. Second-degree atrioventricular heart block after doxapram administration. J Pediatr 1998;133:149-50.
11. Malliard C, Boutroy M, Fresson J, et al. QT interval lengthening in premature infants treated with doxapram. Clin Pharmacol Ther 2001;70:540-5.
12. Gan TJ. "Black box" warning on droperidol: a report of the FDA convened expert panel. [letter] Anesth Analg 2004;98:1809-18.
13. Scuderi PE. You (still) can't disprove the existence of dragons. [editorial] Anesthesiology 2005;102:1081-2.
14. Whyte SD, Booker PD, Buckley DG. The effects of propofol and sevoflurane on the QT interval and transmural dispersion of repolarization in children. Anesth Analg 2005;100:71-7.
15. Stuth EA, Stucke AG, Cava JR, et al. Droperidol for perioperative sedation causes a transient prolongation of the QTc time in children under volatile anesthesia. Pediatr Anaesth 2004;14:831-7.
16. White PF, Song D, Abrao J, et al. Effect of low-dose droperidol on the QT interval during and after general anesthesia. Anesthesiology 2005;102:1101-5.
17. Charbit B, Albaladejo P, Funck-Brentano C, et al. Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron. Anesthesiology 2005;102:1094-100.
18. Kurth J, Maguire G. Pediatric case report of quetiapine overdose and QTc prolongation. Ann Clin Psychiatry 2004;16:229-31.
19. Blair J, Scahill L, State M, et al. Electrocardiographic changes in children and adolescents treated with ziprasidone: a prospective study. J Am Acad Child Adolesc Psychiatry 2005;44;73-9.
20. Sawant S, Daviss SR. Seizures and prolonged QTc with atomoxetine overdose. [letter] Am J Psychiatry 2004;161:757.
21. Slama TG. Minimizing the risk for QT interval prolongation. J Fam Pract 2005 Jun;Suppl:S15-S17.

Pharmacology Literature Review

Ketamine Review

The authors review 12 studies which have evaluated the efficacy and safety of ketamine for sedation of pediatric patients in the Emergency Department. The studies, prospective and retrospective, include sample sizes ranging from 29 to 1,022 children. Efficacy rates ranged from 50% to 100%, with variation in response primarily associated with the ketamine dose used. The most commonly reported adverse effects were emesis, ataxia, decreased oxygen saturation, agitation, or behavioral reactions. Based on their review, the authors concluded that ketamine was an effective agent in this setting, with minimal adverse effects compared to traditional sedatives. They caution, however, that the drug only be used by experienced clinicians with adequate support personnel. Mistry RB, Nahata MC. Ketamine for conscious sedation in pediatric emergency care. **Pharmacotherapy 2005;25:1104-11.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 9/23/05:

1. Duloxetine (Cymbalta®) was added to the Inpatient and Outpatient Formularies. It is used in the treatment of depression and neuropathic pain associated with diabetic peripheral neuropathy.
2. Intramuscular olanzapine (Zyprexa® IM) was added to the Inpatient Formulary, with restriction to approval by Psychiatry attendings, for the treatment of agitation in patients with schizophrenia and bipolar I mania.
3. Treprostinil (Remodulin®) was added to the Inpatient Formulary for the management of pulmonary arterial hypertension.
4. The restriction on dexmedetomidine was amended to include use in the surgical setting for patients undergoing awake craniotomy or complex spinal procedures.
5. The guidelines for use of drotrecogin alfa were amended to remove the requirement for APACHE II scores.
6. The use of generic warfarin was approved.

Contributing Editor:Marcia L. Buck, Pharm.D.
Editorial Board: Kristi N. Hofer, Pharm.D.
Michelle W. McCarthy, Pharm.D.
If you have comments or suggestions for future issues, please contact us at Box 800674, UVA Health System, Charlottesville, VA 22908 or by e-mail to mlb3u@virginia.edu. This newsletter is also available at www.healthsystem.virginia.edu/internet/pediatrics/pharma-news/home.cfm