ABSTRACT. Objectives. Life-threatening arrhythmias and prolonged QT interval have been reported in adults and children using cisapride, a medication structurally similar to procainamide. Premature infants have reduced activity of cytochrome p-450, the system responsible for metabolism of cisapride, which could lead to QT prolongation. Therefore, we prospectively studied premature infants and children receiving cisapride to analyze the effect of prolonged cisapride therapy on QT interval.

Design. Premature infants in a neonatal intensive care unit and children seen at a pediatric gastroenterology clinic in a tertiary care hospital had electrocardiography-analyzed and -corrected QT interval measured before cisapride (0.8/mg/kg per day) therapy, and again after 1 month of therapy. If baseline electrocardiography was not performed initially, it was obtained after cessation of therapy.

Results. A total of 30 children participated in the study. Mean corrected QT interval was similar at baseline and at 1 month after therapy. Significant QT prolongation was not found, and no adverse effects were recorded.

Conclusions. Corrected QT interval during prolonged cisapride therapy at 0.8 mg/kg per day appears to be similar for premature infants and children. An inherent trend toward QT prolongation was not detected in either group. In the absence of other risk factors that alter cisapride metabolism or predispose to arrhythmia, cisapride may be safe for use in premature infants as well as in children. Additional studies are needed to confirm these data. Pediatrics 1998;101(3). URL: http://www.pediatrics.org/cgi/content/full/101/3/e9; cisapride, arrhythmias, QT interval, prematurity, children.

ABBREVIATIONS. ECG, electrocardiography; QTc, corrected QT; 5-HT, 5-hydroxytryptamine.

Cisapride is a prokinetic agent that is commonly used for a variety of motility disorders including gastroesophageal reflux, gastroparesis, and constipation. Between 1993 and 1996, the Food and Drug Administration Medwatch Program reported 57 patients (including 7 children and 1 adolescent) who developed electrocardiographic (ECG) changes, either torsade de points or prolonged QT interval with syncope related to use of cisapride. Ventricular tachycardia occurred in an 8-year-old patient in an intensive care setting receiving cisapride with concomitant erythromycin, and second-degree atioventricular block with prolonged QT was reported in a 2-month-old premature infant receiving cisapride at therapeutic doses. Arrhythmia attributable to cisapride could be caused by an unrecognized inherent trend toward QT prolongation or to coexisting factors such as overdosing or altered metabolism of cisapride. One of the factors implicated thus far has been use of medications that inhibit the cytochrome p-450 system, the primary pathway for cisapride metabolism. Premature infants and neonates may be at higher risk because of reduced activity of the cytochrome p-450 enzymes in this age group. Although case reports of increased QT interval diagnosed attributable to clinical symptoms exist, we are not aware of any prospective study that has looked at the effect of cisapride on QT interval in therapeutic doses. The aim of this study was to evaluate the effect of prolonged cisapride use, at a fixed dose, on corrected QT interval in premature infants and children.

METHODS

Schneider Children’s Medical Center is a tertiary care children’s hospital located in central Israel that treats children and adolescents to 18 years of age. All children followed by the Pediatric Gastroenterology and Nutrition Service Outpatient Clinic or infants hospitalized in the Neonatal Intensive Care Unit, who were receiving or about to start cisapride for a period of at least 1 month, were considered eligible to enter the study. Five children receiving cisapride at therapeutic doses of 0.2 mg/kg/dose four times daily had an ECG performed after their morning dose and another ECG performed at the first follow-up visit after stopping cisapride therapy. Children about to start cisapride had a baseline ECG performed. All children then were scheduled for a follow-up visit 1 month later and had a repeat ECG performed at this time, provided that they had been compliant throughout the study period. Patients were instructed to take their regular dose of cisapride before arriving at the clinic.

All ECG studies were evaluated by a single cardiologist blinded to therapy, and QT interval was documented. Corrected QT interval was calculated according to the Bazett formula in leads L2 or V5. Corrected QT (QTc) was considered prolonged if it exceeded the upper limit for age.

Statistical Analysis

Analysis of variance was performed using the Duncan multiple comparison option. Because of the small number of patients, the Kruskall–Wallis nonparametric test also was performed. To compare means between first dose and 1 month of therapy to baseline QTc interval, the student’s t test also was performed. P values ≤.05 were considered statistically significant.
TABLE 1. Patient Data

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number</th>
<th>Age</th>
<th>Gestational Age</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature</td>
<td>10</td>
<td>3.6 ± 2.5 weeks</td>
<td>32.4 ± 3.1 weeks</td>
<td>Reflux 9, Constipation 0, Other 1</td>
</tr>
<tr>
<td>Children</td>
<td>20</td>
<td>8.4 ± 5.5 years</td>
<td></td>
<td>Reflux 10, Constipation 7, Other 3</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td></td>
<td></td>
<td>Reflux 19, Constipation 7, Other 4</td>
</tr>
</tbody>
</table>

Results are expressed as the mean ± SD.

RESULTS

Patient Data

A total of 38 children and adolescents were enrolled into the study, including 12 premature infants. Seven children were excluded because of noncompliance, and 1 was lost to follow-up.

Indications for cisapride therapy included gastroesophageal reflux, constipation, cyclic vomiting, and anorexia nervosa with early satiety, as well as suspected motility disorder in a premature infant. Data regarding age and the clinical disorder necessitating cisapride therapy are presented in Table 1. Gestational age for premature infants ranged from 25 to 36 weeks. One premature infant had an episode of supraventricular tachycardia before cisapride therapy.

Effect of Cisapride

There were no clinical adverse effects reported during the study. Two infants had received erythromycin for 1 week during therapy, but medication had been discontinued before follow-up, and ECG during erythromycin therapy was not performed. No abnormalities were found on ECG analysis during the study.

Mean QTc interval according to age group and time of ECG study is presented in Table 2. Mean QTc interval at 1 month was almost unchanged compared with baseline in all groups, and the difference was not statistically significant.

Many patients continued cisapride treatment, but additional ECG studies were not performed after the end of the study period.

DISCUSSION

Since reports have started to surface regarding life threatening arrhythmias and QT prolongation in patients using cisapride, concern has arisen regarding the safety of cisapride use. The risk for serious ventricular arrhythmia in an adult population has been estimated to be 1 in 120,000 patients but might be much higher because of underreporting. The risk for silent QT prolongation would be expected to be even higher; however, this has not been examined previously in the published literature. Premature infants theoretically could be a high-risk group. Cisapride is bound to albumin, and hyperbilirubinemia could cause displacement of cisapride. Furthermore, premature infants have lower cytochrome p-450 activity and content relative to older children and adults. These factors could lead to higher blood levels and more toxicity.

In our study, children and premature infants using cisapride at therapeutic doses of 0.8 mg/kg per day did not develop QT prolongation as judged by follow-up ECG. Furthermore, premature infants who theoretically might be at higher risk, did not show a trend to prolongation of QT interval despite prolonged use, and QTc interval was similar for premature and older children at baseline and during therapy. Although the number of patients, and specifically premature infants, was small, these data tend to support the concept that other factors may be responsible for QT prolongation.

The mechanism by which cisapride prolongs QT is not understood. Several theories have been advanced. Cisapride is similar structurally to procarbazine, a class I antiarrhythmic drug that slows conduction velocity, increases the effective refractory period in the His–Purkinje system, and moderately prolongs repolarization. In addition, cisapride is a 5-HT4 agonist, and 5-HT4 receptors have been isolated in human atria, possibly causing a chronotropic effect.

Factors that increase blood levels of cisapride, or, specifically, inhibit cytochrome p-450 IIIA4 (such as macrolide antibiotics, imidazole antifungal agents, and grapefruit juice) may be the most common cause for concern. Patients with diseases predisposing to arrhythmias, such as hypokalemia, hypomagnesemia, or hypoxia, also might be at a higher risk for developing ECG changes. Idiosyncratic reactions may also play a role in isolated cases.

To our knowledge this is the first study that has prospectively followed ECG during use of cisapride in premature infants and children. Although the number of patients in our study was small, the effect of cisapride on QT interval in premature infants was not different than that in older children, and an inherent trend to prolongation of the QT interval during cisapride use was not identified in any age group. Additional studies with larger number of patients are required to confirm the safety of cisapride use in premature infants. Risk factors cited previously should be determined before prescribing this medication, and patients as well as physicians should be warned of medications that might increase cisapride toxicity.
REFERENCES

2. Pettignano R, Chambliss RC, Darsey E, et al. Cisapride-induced dysr-
   rhythmia in a pediatric patient receiving extracorporeal life support.
   Crit Care Med. 1996;24:1268–1271
3. Lewin MB, Bryant RM, Fenrich AL, Grifka RG. Cisapride-induced long
4. Shulman R. Report from the NASPGN Therapeutics Subcommittee: Cisapride
5. Aranda JV, MacLeod SM, Renton KW, Eade NR. Hepatic microsomal
   1974;85:534–542
6. Bazzett HC. An analysis of the time relations of the electrocardiogram.
   Heart. 1920;7:353–370
   1992;305:748–749
   droxytryptamine receptor in human atrium. Br J Pharmacol. 1990;100:
   879–885
10. Kaumann AJ. Do human atrial 5-HT4 receptors mediate arrhythmias?
11. Briejer MR, Akkermans LMA, Schuurkes JAJ. Gastrointestinal proki-
    netic benzamides: the pharmacology underlying stimulation of motility.
    Pharmacol Rev. 1995;47:631–651
QT Interval in Children and Infants Receiving Cisapride
Arie Levine, Rami Fogelman, Leah Sirota, Zili Zangen, Raanan Shamir and Gabriel Dinari
*Pediatrics* 1998;101;e9
DOI: 10.1542/peds.101.3.e9

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://pediatrics.aappublications.org/content/101/3/e9">http://pediatrics.aappublications.org/content/101/3/e9</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 11 articles, 1 of which you can access for free at: <a href="http://pediatrics.aappublications.org/content/101/3/e9.full#ref-list-1">http://pediatrics.aappublications.org/content/101/3/e9.full#ref-list-1</a></td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s): Cardiology <a href="http://classic.pediatrics.aappublications.org/cgi/collection/cardiology_sub">http://classic.pediatrics.aappublications.org/cgi/collection/cardiology_sub</a> Cardiovascular Disorders <a href="http://classic.pediatrics.aappublications.org/cgi/collection/cardiovascular_disorders_sub">http://classic.pediatrics.aappublications.org/cgi/collection/cardiovascular_disorders_sub</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="https://shop.aap.org/licensing-permissions/">https://shop.aap.org/licensing-permissions/</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://classic.pediatrics.aappublications.org/content/reprints">http://classic.pediatrics.aappublications.org/content/reprints</a></td>
</tr>
</tbody>
</table>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 1998 by the American Academy of Pediatrics. All rights reserved. Print ISSN: .
QT Interval in Children and Infants Receiving Cisapride
Arie Levine, Rami Fogelman, Leah Sirota, Zili Zangen, Raanan Shamir and Gabriel Dinari

*Pediatrics* 1998;101;e9
DOI: 10.1542/peds.101.3.e9

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/101/3/e9