Effects of Domperidone on QT Interval in Children with Gastroesophageal Reflux Disease

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Background: Domperidone has been widely used in children with gastroesophageal reflux disease (GERD). Studies on the effects of domperidone on corrected QT interval (QTc) in young children are limited. Our aim was to study the effect of domperidone on the repolarization abnormalities assessed by electrocardiogram (ECG) in young children.

Methods: ECG was performed in children <2 years of age before and after taking domperidone orally 0.3 mg/kg three times/day for at least a 1 week period. Each ECG was reviewed and QT, RR, and Tpeak to Tend Intervals (TpTe) were measured to calculate the QTc and TpTe/QT ratio.

Results: A total of 22 patients (12 male) with a median age of 8.5 months (1–24 months) were enrolled. Most patients (59.1%) were under 1 year of age. The median baseline QTc (410 milliseconds, 350–450 milliseconds) was not significantly different from the QTc after taking domperidone (410 milliseconds, 320–560 milliseconds), p = 0.159. Only two patients showed a QTc increase >450 milliseconds. The baseline TpTe interval and TpTe/QT (105 milliseconds, 60–170 milliseconds and 0.27 milliseconds, 0.15–0.43 milliseconds) were significantly greater than the TpTe interval and TpTe/QT in children after taking domperidone (90 milliseconds, 60–140 milliseconds and 0.22 milliseconds, 0.15–0.29 milliseconds), p = 0.001 and 0.004, respectively.

Conclusions: Our data demonstrate that domperidone treatment over a short-term period in children <2 years of age did not lengthen QTc significantly; however, QTc increased >450 milliseconds in two patients with concomitant lansoprazole. Routine baseline and follow-up ECG may not be necessary in each individual case receiving only domperidone.

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1. Introduction

Domperidone is a dopamine-2 receptor antagonist1–3 and affects the chemoreceptor trigger zone on the fourth ventricle outside the blood brain barrier and the motor function of the stomach and small intestine. In contrast to metoclopramide, domperidone does not cross the blood brain barrier; therefore, neurological side effects such as dystonic reaction are rare. Domperidone is broadly prescribed for acute vomiting, gastroparesis and gastroesophageal reflux disease (GERD), since its safety profiles are more acceptable than metoclopramide and cisapride. The study of domperidone treatment at the dose of 0.3 mg/kg/ageal reflux disease (GERD), since its safety profiles are prescribed for acute vomiting, gastroparesis and gastroesophageal reflux disease are rare. Domperidone is broadly prescribed for acute vomiting, gastroparesis and gastroesophageal reflux disease. The aim of our study was to determine the cardiac effect of short-term oral domperidone on the repolarization abnormalities assessed by measuring QTc and Tpeak to Tend (TpTe) interval on ECG.

2. Patients and methods

Children who were aged <2 years with suspected symptoms of GERD and who required domperidone therapy at a single university hospital were enrolled. Informed consent was obtained from the parents of all patients before enrolment. Domperidone was given at the dose of 0.3 mg/kg before meals three times/day. A 12-lead ECG using paper speed at 25 mm/s or 50 mm/s was obtained in each child at baseline before starting domperidone and at 1 week following domperidone administration. All ECGs were performed without sedation, but all children lay calmly in their mothers’ laps or on beds in a nonagitated state.

2.1. Measurements and calculations

Each ECG was reviewed by a pediatric cardiologist (YB) blinded to the clinical setting. The QT interval, defined as the interval from the beginning of the Q wave to the end of the T wave, the RR interval, defined as the interval from the beginning of the Q wave to the consecutive R wave, and the TpTe interval, defined as the interval from the peak of the T wave to the end of the T wave, were measured in lead II.

The QTc was calculated from Bazett’s formula as the QT interval in seconds divided by the square root of the RR interval in seconds. The prolonged QTc was defined as QTc >440 milliseconds for infants <1 year of age and >450 milliseconds for children aged 1–5 years.4 The normal TpTe interval was 62.4 ± 11 milliseconds (39–97 milliseconds) for children <1 year of age and 67.6 ± 9.2 milliseconds (43–89 milliseconds) for children aged 1–5 years.10 The prolonged TpTe interval was defined as TpTe/QT > 0.21.10 QTc, TpTe interval, and TpTe/QT were compared between, before, and after taking domperidone. Potential factors influencing the effects, such as age, dosage, pre-existing disease, and concomitant medicines, were also evaluated.

2.2. Statistical analysis

Descriptive statistics were calculated and analyzed to express mean, standard deviation (SD), median, range, maximum and minimum value, frequency, percentage, and distribution. Multiple logistic regressions and the Mann-Whitney test were used to find the risk factors related to an abnormal ECG.

3. Results

Twenty-two patients (12 male, 54.6%) with symptoms suspected of GERD were enrolled. The median age was 8.5 months (range 1–24 months) and median weight of 6.3 kg (range 3.2–13.8 kg). Most patients (59.1%) were <1 year old. Concomitant medications consisted of lansoprazole, phenobarbital, vigabatrin, nitrazepam, and vitamins. Seventeen patients received lansoprazole while five patients did not receive this medication. The associated diseases consisted of epilepsy, heart disease, thyrotoxinemia, iron deficiency anemia, cerebral palsy, and hepatitis (Table 1).

The median baseline QTc before taking domperidone was 410 milliseconds (range 350–450 milliseconds). The median QTc after taking domperidone was 410 milliseconds (range 320–450 milliseconds), which was not significantly different from the baseline (p = 0.159). At baseline, only one patient had a QTc of 450 milliseconds. After taking domperidone, her QTc decreased to 400 milliseconds. When the QTc at baseline and after domperidone therapy was compared in each individual patient, an increased from the baseline was seen in eight patients (36%), but only two patients showed an increase in QTc ≥450 milliseconds (Figure 1). Two had a baseline QTc of 420 milliseconds and 440 milliseconds, and after domperidone their QTc increased to 450 milliseconds (Figure 2). Subgroup analysis demonstrated that no factors were associated with increased QTc ≥450 milliseconds, including age, sex, pre-existing disease, and concomitant medicines. Interestingly, two out of 17 patients receiving lansoprazole showed QTc ≥450 milliseconds after domperidone therapy.

<table>
<thead>
<tr>
<th>Underlying diseases</th>
<th>N (%)</th>
<th>Medications</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>1 (7.14)</td>
<td>Lansoprazole</td>
<td>17 (62.96)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>1 (7.14)</td>
<td>Phenobarbital</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>2 (14.29)</td>
<td>Vigabatrin</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>1 (7.14)</td>
<td>Nitrazepam</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>2 (14.29)</td>
<td>Multivitamin</td>
<td>6 (22.22)</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>7 (50.0)</td>
<td></td>
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</tr>
</tbody>
</table>
contrast, none of the five patients without lansoprazole had QTc ≥450 milliseconds after domperidone therapy.

The median baseline TpTe interval and TpTe/QT before taking domperidone were 105 milliseconds (range 60–170 milliseconds) and 0.27 milliseconds (range 0.15–0.43 milliseconds), respectively. Interestingly, the median TpTe interval and TpTe/QT after taking domperidone were 90 milliseconds (range 60–140 milliseconds) and 0.22 milliseconds (range 0.15–0.34 milliseconds), which were significantly less than before taking domperidone, p = 0.001 and 0.004, respectively. The TpTe interval (Figure 3) and TpTe/QT (Figure 4) decreased after taking domperidone in most patients.

4. Discussion

Currently, domperidone is widely prescribed for children <2 years old with GERD. Although proton pump inhibitors are the treatment of choice for GERD in children, prokinetics may be of benefit to some patients who do not have an adequate therapeutic response to proton pump inhibitors. When prokinetics are indicated, domperidone is preferred, due to an awareness of the side effects of the others. Rocha and Barbosa4 reported prolongation of the QT interval after oral use of high-dose domperidone in a 4-month-old infant, which was normalized after discontinuation. The authors recommended obtaining 12 ECGs both before and after taking domperidone. Djeddi et al6

Figure 1  Linear graph comparing corrected QT interval (QTc) in milliseconds before and after taking domperidone in each patient.

Figure 2  Electrocardiogram tracing showing measurement of T_peak to T_end (TpTe), QT, and RR interval in lead II. (A) One patient with corrected QT interval (QTc) increased from 420 milliseconds to 450 milliseconds; (B) one patient with QTc increased from 440 milliseconds to 450 milliseconds.
reported that QTc increased more than 12 milliseconds in 48% of 31 infants treated with domperidone. The risk factors for domperidone-induced QTc prolongation identified in this study were advanced gestational age and hyperkalemia. Günlêmez et al. demonstrated that domperidone therapy in modest doses (0.25 mg/kg four times/day) in premature infants was safe except in two out of 40 infants who developed QTc prolongation above 450 milliseconds without clinical arrhythmia. Most patients had baseline QTc interval and QTc/QT ratio higher than the referenced values. Surprisingly, our study demonstrated that QTc interval and QTc/QT in lead II after taking domperidone were very limited. Most patients had baseline QTc interval and QTc/QT ratio higher than the referenced values. The TpTe interval is an index of transmural dispersion of repolarization and spatial dispersion of repolarization index. Prolongation of this interval has been reported to predispose to life-threatening ventricular arrhythmias in long QT syndrome, polymorphic catecholaminergic ventricular tachycardia, Brugada syndrome, and short QT syndrome, and it could be an indicator of increased risk of sudden cardiac death. Measurement of the TpTe interval in such children may be an indicator for potential ventricular arrhythmias. The long TpTe interval has been associated with cardiac arrhythmia. Interestingly, the TpTe/QT ratio has been shown to be an electrocardiographic index of arrhythmogenesis. There were increased chances of cardiac arrhythmia and ventricular tachycardia in patients with long QT syndrome, Brugada syndrome, short QT syndrome, and in those with organic heart diseases such as acute myocardial infarction, if their TpTe/QT values in lead II were greater than the 98th percentile or 0.21 despite normal QTc. Functional reentry is the underlying mechanism for arrhythmogenesis associated with an increased TpTe/QT ratio. The studies on TpTe interval and TpTe/QT ratio in children taking domperidone are very limited. Most patients had baseline TpTe interval and TpTe/QT ratio higher than the referenced values. Experimental study has demonstrated that domperidone can prolong cardiac repolarization by blocking the rapid component (Ikr) of the delayed rectifier potassium current. The cardiac electrophysiological effects are similar to those of cisapride. Excessive Ikr block may lead to triggering tachyarrhythmia and sudden death. Pediatricians should aware of potential cardiac side effects of domperidone particularly when prescribing high doses, or using concomitant medications known to increase QT interval, and drugs that inhibit P450 enzyme, which are important for drug clearance.

5. Conclusions
In summary, domperidone treatment over a short-term period in children <2 years of age did not significantly
lengthen QTC. Based on the results of the current study, the routine baseline and follow-up ECG may not be generally necessary in each individual case receiving only domperidone. However, further studies with larger sample sizes are required to confirm this suggestion.

Conflicts of interest

The authors declare no conflicts of interest.

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References


