ORIGINAL ARTICLE

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 T_{peak} to T_{end} 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 $\geq$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 $\geq$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 antagonist[1−3] 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/dose in 13 newborns demonstrated no serious side effects.[2] However, Rocha and Barbosa[4] reported a QT prolongation in a 4-month-old infant receiving a high dose of 0.6 mg/kg three times/day. In addition, domperidone caused QT prolongation in patients who received concomitant treatment with ketoconazole.[5] There were few research studies of the side effects on electrocardiogram (ECG) in children and the results were controversial. Djeddi et al[6] reported QT prolongation in 31 infants with gastroesophageal reflux treated with domperidone. The study by Günlemez et al[7] showed no difference of corrected QT before and after domperidone therapy in 40 premature infants, except for two babies who developed corrected QT interval (QTc) prolongation. 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 T_{peak} to T_{end} (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 preceding R 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[8] 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.[9] 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. In

Table 1	Underlying diseases and concomitant medications.		
Underlying diseases	N (%)	Medications	N (%)
Seizure	1 (7.14)	Lansoprazole	17 (62.96)
Thyroid disease	1 (7.14)	Phenobarbital	2 (7.4)
Iron deficiency	2 (14.29)	Vigabatrin	1 (3.7)
Chronic liver disease	1 (7.14)	Nitrazepam	1 (3.7)
Heart disease	2 (14.29)	Multivitamin	6 (22.22)
Cerebral palsy	7 (50.0)		