Journal of Perinatology (2010) 30, 50–53

www.nature.com/jp

JPER Open

ORIGINAL ARTICLE

Effect of domperidone on the QTc interval in premature infants

A Günlemez[1], A Babaoğlu[2], AE Arısoy[1], G Türker[1] and AS Gökalp[1]

[1]Section of Neonatology, Department of Neonatology, Kocaeli University Faculty of Medicine, Kocaeli, Turkey and [2]Section of Pediatric Cardiology, Department of Pediatrics, Kocaeli University Faculty of Medicine, Kocaeli, Turkey

Objective: To evaluate the effect of domperidone use on corrected QT interval in premature infants.

Study Design: A prospective study of premature infants receiving domperidone was included in this study. A baseline electrocardiogram was obtained just before and 3, 7 and 14 days after initiation of domperidone. Corrected QT was considered prolonged if it exceeded the upper limit for age.

Result: A total of 40 premature infants were enrolled in this study. The mean birth weight of 1109 ± 332 g, mean gestational age of 28.8 ± 2.4 years and mean age at the onset of domperidone were 32.8 ± 2 days. No difference in corrected QT interval was observed between just before and 3, 7 and 14 days after the start of the treatment. Two infants had corrected QT interval prolongation without any clinical side effect that resolved spontaneously.

Conclusion: Our experience suggests that domperidone administered cautiously in modest doses does not result in arrhythmias or conduction defects in premature infants statistically. Additional data are needed to give optimal advice regarding the safety of domperidone treatment in premature infants.

Journal of Perinatology (2010) **30,** 50–53; doi:10.1038/jp.2009.96; published online 23 July 2009

Keywords: domperidone; gastroesophageal reflux; premature; infant; arrthythmia; long QT

Introduction

Domperidone is a prokinetic agent that is commonly used for a variety of motility disorders including gastroesophageal reflux and constipation. It has been in the market worldwide since 1978. Chemically distinct from cisapride, domperidone is a peripheral dopamine 2-receptor antagonist. Unlike metoclopramide, another prokinetic dopamine-receptor antagonist, domperidone does not readily cross the blood–brain barrier and reports of adverse effects on the central nervous system, such as dystonic reactions, are rare.[1,2] On account of its apparent favorable safety profile, domperidone might seem to be safer as an alternative to cisapride and metoclopramide.

However, QT interval (QT) prolongation and life-threatening ventricular tachyarrhythmias have been reported with domperidone.[2–6] Domperidone possesses cardiac electrophysiological effects similar to those of cisapride and class III antiarrhythmic drugs. These effects are observed at clinically relevant concentrations of the drug. The experimental studies carried out by Drolet *et al*.[7] showed that domperidone can prolong cardiac repolarization in a reverse rate-dependent manner by blocking the cardiac potassium current (IKr: rapidly activating delayed rectifier K^+ current). Excessive IKr block may lead to triggered tachyarrhythmias and sudden death.[8] The study by Drolet *et al*.[7] provided a new explanation for QT prolongation and ventricular tachyarrhythmia during domperidone treatment. Domperidone should be one of the next compounds to add to the growing list of drugs associated with acquired long QT syndrome. Therefore, domperidone should not be considered a no-risk alternative to cisapride.

In the literature, no systematic study has been performed to evaluate the effect of domperidone on the QT interval in premature infants. Premature infants and neonates may be at higher risk because of the reduced activity of the cytochrome p450 enzymes in this age group.[7–9] These cardiac side effects should be evaluated because the restrictions on cisapride have resulted in the overuse of domperidone.

The aim of this study was to evaluate the effect of domperidone use on corrected QT (QTc) interval in premature infants.

Methods

The prospective study was carried out in our neonatal unit from January 2006 until August 2008. All infants with a gestational age of $\leqslant$34 weeks admitted to the unit who decided to start domperidone treatment were included in this study. All premature infants who had not reached the postconceptional age of 37 weeks at that time were eligible. Exclusion criteria for QTc interval analysis was either increased QTc interval ($\geqslant$0.45) before domperidone administration or a family history of long QT

Correspondence: Dr A Günlemez, Section of Neonatology, Cumhuriyet Mahallesi, Sahil Caddesi, Deniz Sokağı B Blok D 6, İzmit, 41100 Kocaeli, Turkey.
E-mail: aylagunlemez@yahoo.com
Received 21 March 2009; accepted 14 May 2009; published online 23 July 2009

syndrome, sudden death or the existence of well-known conditions that could increase the QTc interval, for example, electrolyte abnormalities, hypothyroidism, intracranial disorders, renal or hepatic abnormalities and those using a macrolide antibiotic or azole antifungal at any stage during the study. A blood test for potassium, calcium and magnesium levels was available for all the infants included in the survey. Congenital hypothyroidism was excluded in all infants by dosage with thyrotrophin and thyroid stimulating hormone on day 7, as part of the neonatal screening procedure for premature infants. For each infant, birth weight, gestational age, small for gestational age, postnatal age, postconceptional age, weight on the day of the start of treatment and associated treatments were recorded. Each infant acted as its own control.

Domperidone was started in the dose of $0.25\,mg\,kg^{-1}$ every 6 h before feeding. The drug was always given through the gastrointestinal tract, orally or through a nasogastric tube. They were reweighed after 7 days and the dose was adjusted for their new weight. A base-line electrocardiogram (ECG) was obtained just before starting domperidone. Follow-up ECG was obtained 3, 7 and 14 days after the initiation of therapy. All infants were placed on continuous bedside ECG monitoring, which is standard in a neonatal intensive care unit during the entire hospitalization period. ECG was performed with a Hewlett–Packard Page Writer 100 model (Hewlett–Packard, Bracknell, UK) M1705B, with a paper speed of $25\,mm\,s^{-1}$ to allow a precise measure of QTc interval. All ECG studies were evaluated by a single cardiologist who was blinded both to the patients and the frequency of administration of domperidone. QT interval was corrected for the heart rate using Bazzet's formula ($QTc = QT/\sqrt{R-R}$) in five non-consecutive beats using lead II, and five values were then averaged. The longest QT interval was also identified on each ECG. Corrected QT was considered prolonged if it exceeded the upper limit for age (QTc interval $\geqslant 0.45\,s$).[10]

The study protocol was approved by the hospital's research, scientific and ethics committee. Parents' informed consent was taken for all eligible infants.

Statistical analysis

Statistical analysis was performed using a standard commercial software package (SPSS version 13.0, SPSS Inc., Chicago, IL, USA). Descriptive analysis was presented as the mean ± s.d. Comparisons between QTc interval before and after domperidone were performed by the analysis of variance followed by the Fisher's least significant difference test. Inter-subgroup comparisons were performed by Student's *t*-test. A *P*-value of <0.05 was considered statistically significant.

Results

A total of 43 premature infants were enrolled in the study. Three infants were excluded because of the concomitant prescription of drugs known to increase the QTc interval. Indications for domperidone treatment included severe gastroesophageal reflux disease with feeding intolerance, apnea, bradycardia episodes and suspected intestinal motility disorder in premature infants.

The neonates included in our study were born between 24 and 33 weeks of gestational age (mean: 28.8 ± 2.4 weeks), weighing between 600 and 1760 g (mean: 1109 ± 332 g). On the first day of domperidone treatment, the mean postnatal age was 32.8 ± 2 days. Patient characteristics are given in Table 1.

No difference in QTc interval was observed between just before and 3, 7 and 14 days after the start of treatment. The mean QTc interval before and after 3 days, before and after 7 days, and before and after 14 days of domperidone was similar ($P = 0.469$, $P = 0.940$ and $P = 0.951$, respectively) (Table 2). The QTc interval increased to above 0.45 in two infants at day 7 on domperidone treatment. The gestational age of these infants was 26 and 30 weeks and the QTc intervals were 0.49 and 0.46 s at day 7. However, this prolongation of QTc interval was not associated with the occurrence of rhythm disorders. QTc prolongation returned to

Table 1 Characteristics of patients treated with domperidone ($n = 40$)

	Study group (n = 40)
Gestational age mean ± s.d. (week)	28.8 ± 2.4 (24–33)
Birth weight (g) mean ± s.d.	1109 ± 332 (600–1760)
Male *n* (%)	65 (67)
Small for gestational age	5 (12.5)
Age at onset of domperidone (day)	31.7 ± 9.8
Mean postconceptional age (weeks)	32 ± 2 (29–35)
Mean weight at onset of domperidone (g)	1392 ± 390

Table 2 Evaluation of QTc interval before and during domperidone administration ($n = 40$)

	QTc at baseline	*QTc at day 3*	*QTc at day 7*	*QTc at day 14*	P-*value**
Mean QTc interval (s) (s.d.)	0.37 ± 0.03	0.38 ± 0.03	0.37 ± 0.04	0.37 ± 0.03	0.877
Number with increase in QTc (*n*)	0	0	2	0	—
Number with arrhythmia (*n*)	0	0	0	0	—

Abbreviation: QTc, corrected QT interval.
*0–3 day, $P = 0.469$; 0–7 day, $P = 0.940$; 0–14 day, $P = 0.951$.

0.35 and 0.38 s, respectively, on discontinuation of the drug. Also, during their stay in our neonatal unit, no cardiac arrhythmias or atrioventricular conduction abnormalities by bedside ECG monitoring were seen in any of the study infants.

Discussion

Gastroesophageal reflux (GER) and GER disease occur frequently during the first months of life. Owing to the immaturity of the esophagus and stomach, some complications of GER occur more frequently especially in preterm infants. In preterm infants, empiric therapy is often administered using the agents of unproven efficacy and safety to treat symptoms that are likely unrelated to GER. In a survey on management practices for GER in preterm infants, the common treatment strategies included are positioning, feed thickeners, histamine2 receptor antagonists, antacids, prokinetics, proton pump inhibitors and dopamine receptor antagonists. The safety, efficacy and appropriate dosing recommendations for most medical therapies remain uncertain in neonates.[11,12]

There are limited studies evaluating the efficacy and adverse effects of domperidone in a neonatal population. Clinical attention should be directed toward QT prolongation and proarrhythmic events when domperidone is administered, as it was with cisapride, because domperidone is a potent IKr blocker.[7] K^+ channel expression and activity are particularly sensitive to the changes during development.[13,14] Wang *et al.*[13] have found that in a neonatal mouse heart, novel expression of the ATP regulated K^+ channel at early and late stages of embryonic development, which may indicate a functional role for this channel during morphogenesis of the heart and Ikr, has a more prominent role in the cardiac conduction system than it does in the adult mouse heart. These results may be important to the preterm and newborn infant in clinical practice.

These potentially significant side effects of domperidone can increase with the concomitant prescriptions known to increase the QT interval. In the neonatal intensive care unit, other IKr blockers such as class III antiarrhythmic drugs and drugs that inhibit P450 enzyme, which are important for drug clearance, can be commonly used. In addition, the P450 system seems to be less developed in the preterm infant, and so the risk of toxicity is high.[9,14] Dailly *et al.*[15] showed that there is no clinically relevant change in domperidone elimination in preterm neonates. However, therapeutic concentrations can be different between adults and preterm neonates.

Earlier reports of domperidone cardiac toxicity suggest that domperidone may not always be safe in some small children and that the use of concomitant medications or some conditions may cause QTc prolongations.[7,9,16–19] In a recent study, Djeddi *et al.*[20] reported QT prolongation in infants treated with domperidone. Mean QTc prolongation was 0.14 s and only one infant developed a QTc of longer than >0.45 s. This study showed a significant association between oral domperidone and QTc prolongation in the infants' group with a gestational age of $\geqslant 32$ weeks, but not in the group with a gestational age of <32 weeks.

In our study, administering a daily dose of 0.25 mg kg^{-1} every 6 h of domperidone treatment did not affect the QTc interval in premature infants statistically. However, for the general population in premature infants, these studies do not imply that there is no risk associated with domperidone-induced increase in QTc, as two infants in this study had QTc interval prolongation. Additional data are needed to give optimal advice regarding the safety of domperidone treatment in premature infants. Owing to the insufficiency of clinical studies related to domperiodone in premature infants and the potential cardiac side effects of the drug, treatment should be chosen carefully and the patient should be observed for QT prolongation from the beginning of the treatment.

Conflict of interest

The authors declare no conflict of interest.

References

1 Barone JA. Domperidone: a peripherally acting dopamine2-receptor antagonist. *Ann Pharmacother* 1999; **33**: 429–440.
2 Rocha CMG, Barbosa MM. QT interval prolongation associated with the oral use of domperidone in infant. *Pediatric Cardiol* 2005; **26**: 720–723.
3 Bruera E, Villamayor R, Roca E, Barugel M, Tronge J, Chacon R. QT interval prolongation and ventricular fibrillation with i.v. domperidone. *Cancer Treat Rep* 1986; **70**: 545–546.
4 Osborne RJ, Slevin ML, Hunter RW, Hamer J. Cardiac arrhythmias during cytotoxic chemotherapy: role of domperidone. *Hum Toxicol* 1985; **4**: 617–626.
5 Cameron HA, Reyntjens AJ, Lake-Bakaar G. Cardiac arrest after treatment with intravenous domperidone. *Br Med J* 1985; **290**: 160.
6 Quinn N, Parkes D, Jackson G, Upward J. Cardiotoxicity of domperidone. *Lancet* 1985; **2**: 724.
7 Drolet B, Rousseau G, Daleau P, Cardinal R, Turgeon J. Domperidone should not be considered a no-risk alternative to cisapride in the treatment of gastrointestinal motility disorders. *Circulation* 2000; **102**(16): 1883–1885.
8 Priori SG. Exploring the hidden danger of noncardiac drugs. *J Cardiovasc Electrophysiol* 1998; **9**: 1114–1116.
9 Tréluyer JM, Rey E, Sonnier M, Pons G, Cresteil T. Evidence of impaired cisapride metabolism in neonates. *Br J Clin Pharmacol* 2001; **52**(4): 419–425.
10 Schwartz PJ, Montemerlo M, Facchini M, Salice P, Rosti D, Poggio G *et al.* The QT interval throughout the first 6 months of life: a prospective study. *Circulation* 1982; **66**(3): 496–501.
11 Vandenplas Y, Salvatore S, Hauser B. The diagnosis and management of gastro-oesophageal reflux in infants. *Early Hum Dev* 2005; **81**(12): 1011–1024.
12 Pritchard DS, Baber N, Stephenson T. Should domperidone be used for the treatment of gastro-oesophageal reflux in children? Systematic review of randomized controlled trials in children aged 1 month to 11 years old. *Br J Clin Pharmacol* 2005; **59**: 725–729.
13 Wang L, Feng ZP, Kondo CS, Sheldon RS, Duff HJ. Developmental changes in the delayed rectifier K channels in mouse heart. *Circ Res* 1996; **79**: 79–85.
14 Davies MP, An RH, Doevendans P, Kubalak S, Chien KR, Kass RS. Developmental changes in ionic channel activity in the embryonic murine heart. *Circ Res* 1996; **78**(1): 15–25.

15 Dailly E, Drouineau MH, Gournay V, Rozé JC, Jolliet P. Population pharmacokinetics of domperidone in preterm neonates. *Eur J Clin Pharmacol* 2008; **64**(12): 1197–1200.

16 Bruera E, Villamayor R, Roca E, Barugel M, Tronge J, Chacon R. Q-T interval prolongation and ventricular fibrillation with i.v. domperidone. *Cancer Treat Rep* 1986; **70**(4): 545–546.

17 Cameron HA, Reyntjens AJ, Lake-Bakaar G. Cardiac arrest after treatment with intravenous domperidone. *Br Med J (Clin Res Ed)* 1985; **12**(290): 160.

18 Critchley P, Langdon N, Parkes JD, Quinn NP, Shindler JS, Marsden CD. Domperidone. *Br Med J (Clin Res Ed)* 1985; **9**(290): 788.

19 Osborne RJ, Slevin ML, Hunter RW, Hamer J. Cardiotoxicity of intravenous domperidone. *Lancet* 1985; **17**(2): 385.

20 Djeddi D, Kongolo G, Lefaix C, Mounard J, Léké A. Effect of domperidone on QT interval in neonates. *J Pediatr* 2008; **53**(5): 663–666.