Türk Kardiyol Dern Arş 1999; 27: 244-247

The Effects of Cisapride on Ventricular Repolarization in Children

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ÇOCUKLARDA SİSAPRİD'IN VENTRİKÜLER REPOLARİZASYON ÜZERİNE ETKİLERİ

ÖZET

Gastrointestinal motiliteyi kolaylaştıran bir ilaç olan sisaprid kullanan erişkin ve çocuklarda başlıca QTc uzamasına bağlı olduğu düşünülen ciddi ventriküler disritmiler bildirilmiştir. Son yıllardaki olgu bildirilerinde bu disritmilerin sisaprid ile birlikte alınan ve sisapridin sitokrom P-450 metabolizmasını inhibe eden ilaçların varlığında ortaya çıktığı vurgulanmıştır. Bu çalışmada yalnız sisaprid tedavisi alan çocuklarda, sisapridin ventriküler repolarizasyon üzerine olan etkileri prospektif olarak incelendi.

Sisaprid tedavisi (0.8-1.2 mg/kg/gün) öncesi ve tedavinin 3., 7., günlerinde ve 1. ayında 20 hastada (ortalama yaş: 6.1±4.1 yıl) 12-derivasyonlu dinlenim EKG'si çekildi. EKG'lerden düzeltilmiş QT aralığı (QTc), QT ve QTc dispersiyonu (QTD, QTcD) hesaplandı. Sonuçlar 372 sağlıklı çocuğun değerleriyle karşılaştırıldı.

Çalışma döneminde hiçbir hastada çarpıntı, presenkop, senkopu da içine alan herhangibir yan etki gözlenmedi. Sisaprid tedavisi öncesi ölçülen QTc, QTD ve QTcD değerleri kontrol grubundan farklı değildi. Tedavinin 7. günü ve 1. ayındaki ortalama QTc kontrol grubuna göre anlamlı yüksekti (sırasıyla p<0.01 ve <0.001). Tedavinin 7. günü ve 1. ayındaki ortalama QTc, tedavi öncesi değere göre de anlamlı yüksek bulundu (sırasıyla p<0.05 ve <0.01). Tedavi sırasındaki ortalama QTD ve QTcD değerleri kontrol grubuna ve tedavi öncesi değerlere göre farklılık göstermiyordu.

Bu çalışmanın sonuçları sisaprid tedavisinin çocuklarda ventrikül repolarizasyonunun uzamasına yol açabileceğini, ancak repolarizasyonda heterojeniteye neden olmadığını gösterdi. Hastaların tümü asemptomatik olduğundan bu uzamanın klinik öneminin olup olmadığı hakkında bir sonuca varılamadı.

Anahtar kelimeler: *Sisaprid, disritmi, QT aralığı, QT dispersiyonu*

Alındığı tarih: 8 Ocak 1999, revizyon 19 Şubat 1999
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Bu çalışmanın bir kısmı "VI th Balkan Pediatric Cardiology & Cardiac Surgery Congress, 4-7 October 1998, Antalya'da sunulmuştur.

Cisapride is a newly developed gastrointestinal prokinetic agent that promotes motility in all segments of the gastrointestinal tract by increasing the release of acethylcoline from postganglionic nerve endings of the myenteric plexus [1]. It has been widely used in various gastrointestinal conditions including gastroesophageal reflux, functional dyspepsia, chronic pseudoobstuction and chronic constipation [2]. Early reports suggested that adverse effects of cisapride were minimal and relatively benign [3,4]. However, serious cardiac dysrhythmias such as polymorphic ventricular tachycardia mainly attributed to inappropriate lengthening of the QT interval have been reported in adults and children during cisapride therapy [5-7]. Most of the reported patients with ventricular dysrhythmias or prolonged QT interval, had been taking concomitant medications of the imidazole class (ketoconazole, fluconazole, itroconazole and metronidazole) or macrolide antibiotics (erythromycin and clarithromycin), which have been found to inhibit the hepatic microsomal P-450 IIIA4 enzyme system [6,8]. Cisapride is metabolized by P-450 IIIA4, thus the blockage of this system results in elevated serum levels of cisapride that leads to cardiac dysrhythmias [8]. On the other hand, prolonged QT interval and serious dysrhythmias have been observed in some patients receiving clinically recommended doses of the drug [5].

A few prospective clinical studies investigating the effect of cisapride on QT interval in children has been done, recently [9-11]. Patient population receiving cisapride was not homogenous in these studies. Some of the patients had been taking medications or had some illnesses that altered cisapride metabolism. Therefore, we prospectively studied infants and children receiving cisapride without any concomitant drug, to analyze the time-related effects of cisapride on ventricular depolarization.

PATIENTS and METHODS

Standard 12-lead resting electrocardiograms (ECGs) were obtained from 25 patients (mean age: 6.1±4.1 years; range 2 months- 13 years) before cisapride (0.8-1.2 mg/kg per day) therapy, and after 3rd, 7th days and 1 month of therapy. Indications of cisapride therapy included gastroesophageal reflux, chronic constipation and cyclic vomiting. Most of the patients were followed on outpatient basis. Patients who needed another drug for intercurrent illness during the study period were excluded. Twenty patients completed the study and the results of them are given. No patient had renal or hepatic dysfunction and electrolyte abnormalities (hypokalemia, hypocalcemia) at the beginning and at the end of the study. Measurements were carried out from standard 12 lead ECGs recorded at a speed of 25 mm/s at rest. A three-channel electrocardiographic recorder (Hewlett Packard, model 4745 A) was used. The QT and preceding RR intervals of at least one sinus beat (range 1-3) were measured in a range of 9 to 12 leads, and the mean QT and RR intervals were calculated for each lead. The corrected QT interval was calculated by the method of Bazett ($QTc = QT / \sqrt{RR}$) [12]. The QT and RR intervals were measured manually with calipers by a single observer. QT intervals were measured from the onset of the QRS complex to the end of the T wave. The end of the T wave was defined as the point of return to the isoelectric line. When a U wave was present, the QT interval was measured to the nadir of the curve between the T and U wave [13]. Dispersion of the QT and QTc (QTD, QTcD) were defined as the difference between the maximum and minimum QT and QTc intervals occurring in any of the 12 leads [14]. Data from these study patients were compared with a control group of 372 normal children [15].

All data are expressed as mean ±SD. Paired and unpaired Student's t test were used where appropriate. A two-tailed p value < 0.05 was considered statistically significant.

RESULTS

There were no clinical adverse effects including palpitations, presyncope and syncope reported during the study period. Since infants obviously cannot verbally communicate a sensation of palpitation or presyncope we only asked to the parents whether their babies had had syncope or not. Mean QTc, QTD and QTcD values of the patients and controls and the time of the ECG study are presented in the Table. Baseline mean QTc, QTD and QTcD measurements were not different from control group. Mean QTc measurements at 3rd day of cisapride treatment were also not different from baseline values and controls. Mean QTc values at 7th day and 1 month of cisapride therapy were significantly higher from control group ($p < 0.01$ and < 0.001, respectively). Mean QTc at 7th day and 1 month of therapy were also found significantly higher than that of baseline value ($p < 0.05$ and < 0.01, respectively). Mean QTD and mean QTcD values during the cisapride treatment were not different from baseline values and controls. Only two patients (2 and 8 months old) had prolongation of QTc (> 450 ms) at 1 month of therapy. One patient had increased QTD (> 50 ms), and 3 patients had increased QTcD (> 80 ms) according to upper limits of control group.

DISCUSSION

Prolongation of QTc, whether congenital in nature or acquired, may cause ventricular tachydysrhythmias, in particular torsades de pointes, syncope and sudden death [16]. Cisapride is a widely prescribed drug for gastrointestinal motility disorders. After marketing of cisapride, possible cardiac side effects were suggested in adult patients who had palpitations, tachycardia or extrasystoles during cisapride therapy [17]. Life-threatening dysrhythmias (torsades de pointes, second-degree heart block) associated with a prolonged QT interval have been reported in adults and children [5-7]. Between 1993 and 1996 the Food and Drug Administration MedWatch Program reported 57 patients (including 7 children and one adolescent) who developed ECG changes, either tor-

Table 1. Mean QTc, QTD, and QTcD values calculated from ECGs, which were obtained before cisapride, and after 3rd, 7th days and 1st month of therapy

	Mean QTc (ms)				Mean QTD (ms)				Mean QTcD (ms)			
	Basal	3rd day	7th day*	1 month#	Basal	3rd day	7th day*	1 month#	Basal	3rd day	7th day*	1 month#
Patients (n:20)	406.5± 21.7	406.1± 22.9	412.3± 28.4	428.2± 18.3	33.5± 12.3	32.9± 12.1	31.5± 9.9	33.0± 14.9	49.8± 11.9	50.7± 15.9	50.5± 14.8	51.6± 27.2
Controls (n:372)	398.7± 19.7				29.9± 10.2				47.3± 16.6			

** 7th day mean QTc vs controls $p < 0.01$, vs baseline $p < 0.05$*
\# 1st month mean QTc vs controls $p < 0.001$, vs baseline $p < 0.01$

sades de pointes or prolonged QT interval with syncope related to use of cisapride. There were 4 deaths, and 16 cardiac arrest responded to resuscitation. Thirty-two of the 57 patients were also taking medications of imidazole class or macrolide antibiotics [6].

The mechanism for the proarrhythmic effects of cisapride has recently been described. Cisapride was shown to be a specific and potent inhibitor of the rapid delayed rectifier potassium current (I_{kr}) in isolated guinea pig hearts and potassium channel transfected cell lines [18,19]. Thus, it causes prolongation of ventricular repolarization. This action is similar to the type 2 hereditary form of long QT syndrome, in which HERG gene is defective [18].

Three prospective studies regarding the effects of cisapride on QT interval in children have been reported in 1998 [9-11]. Levine et al found that mean QTc was similar at baseline and at 1 month after cisapride therapy in 30 infants and children. They concluded that in the absence of other risk factors that alter cisapride metabolism or predispose to arrhythmias, cisapride may be safe for use in infants and children [9]. Khongphatthanayothin et al found 12 % incidence of QTc prolongation in children while using cisapride. However, this result not only attributed to cisapride, because other factors (such as drugs, heart and liver diseases) that might contribute to a long QT were found in 85 % of these patients [10]. Laneau et al showed 11 (31 %) of 35 patients receiving cisapride had a prolonged QTc (> 450 ms). Of the 11 children, only 2 had documented torsades de pointes. Both were taking cisapride concomitantly with a macrolide antibiotic [11].

The results of our study suggest that cisapride does not have an effect on ventricular repolarization at early phase of treatment. However, it may cause slight prolongation of ventricular repolarization after the first week of treatment in infants and children. This prolongation is more profound at 1 month of therapy. Why cisapride has lack of effect on ventricular repolarization at early phase of therapy may be fully understood after pharmacokinetic studies. Only two of the study patients had prolonged QTc (470 and 450 ms) while using cisapride, both were asymptomatic without signs of dysrhythmia. QT interval dispersion is an indirect measure of the heterogeneity of ventricular depolarization [14]. Previous studies showed that increased QT interval dispersion has been associated with an increased risk of malignant ventricular dysrhythmias and sudden death [13,14,20]. We recently proposed that as calculation of QTc dispersion is affected by sinus arrhythmia, which is common in childhood, QT dispersion should not be corrected for heart rate in children [15]. Because 55 % of patients in our cisapride treated group had sinus arrhythmia, we both used QT and QTc dispersion as markers of ventricular repolarization inhomogeneity. There does not appear to be increased heterogeneity of repolarization in our small study group. Laneau et al also reported that cisapride did not cause increased QT and QTc dispersion [11].

Although cisapride, when used alone, may cause slight prolongation of QTc interval without causing increased heterogeneity of repolarization, clinical significance of this prolongation is unclear, because all the patients in this study group have been asymptomatic without signs of dysrhythmia. However potential dysrhythmia risk of cisapride should be under consideration, and we suggest that QT intervals be monitored routinely in children maintained on cisapride, particularly in case of other concurrent illnesses (hepatic, renal, cardiac) or concomitant use of other drugs that alter cisapride metabolism or affect ventricular repolarization.

One of the potential limitations of this study is the small sample size. We are not certain whether patients complied with cisapride therapy fully, so it would have been superior if we had determined the serum cisapride levels during the study period. Thus, we think that largerscale prospective studies investigating the effects of certain variables (cisapride dose, serum drug level, age and sex of the patient) on ventricular repolarization are necessary in children treated with cisapride.

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