

# Efficacy and Side Effects of Cisapride and Metoclopramide in Children with Gastroesophageal Reflux Disease (GERD)

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**KEY WORDS:** Cisapride, Efficacy, Gastroesophageal reflux, and Metoclopramide

## ABSTRACT

**Background:** Gastroesophageal reflux is a common problem in children, and (Gastroesophageal reflux disease) GERD comprises its objective pathologic sequelae, but the term has also been used more recently to denote symptoms affecting quality of life. The Clinical presentation is very variable. It causes mortality and morbidity without appropriate treatment plan.

**Objective:** We are going to evaluate the efficacy of cisapride and metoclopramide in children with gastroesophageal reflux (GERD). In addition, these patients were followed carefully for serious adverse drug reactions.

**Material and methods:** The current prospective study was performed from December 2005 to March 2007 in Children's hospital medical center, involving 130

patients who diagnosed as GERD and their ages were between 1 month to 12 years; they were selected for prokinetic therapy. The response to treatment was evaluated by symptom improvement, and serious adverse drug reaction was demonstrated.

**Findings:** The patients were divided into two groups. The first group was included 104 cases (68 female and 36 male) received cisapride(0.6 mg/kg/day divided in 3 doses in liquid form), and the second group, ( 13 female and 13 male),26 patients, were treated with metoclopramide( 1mg/kg/day divided in 3 doses in drop form). There was no statistical significant difference for absence or presence of esophagitis and it's severity in endoscopic and histologic examinations between two groups. As a matter of fact, almost 70% of the cases were treated with acid-lowering agents simultaneously. In the first group, ECG was recorded before treatment as well as 48-72 hours and 12 weeks after treatment. ECG showed Q-Tc interval prolongation in 4.8% of the first group 48-72 hours after treatment. Moreover, we ob-

served extrapyramidal reactions in 7.7% of the second group. There were no statistically significant differences between two groups in terms of efficacy 2, 4, and 8 weeks after treatment, however there was significantly better response after 12 weeks in cases who received cisapride (P value=0.032).

**Conclusion:** This study revealed that cisapride is a safe medicine for GERD in children considering appropriate cautions. Furthermore, its efficacy was comparable with metoclopramide in short period, but it became much better with continuing treatment.

## INTRODUCTION

Gastroesophageal reflux disease (GERD) now comprises the most common esophageal disorder. It may present as regurgitation, esophageal (irritability, anemia or excessive crying), neurobehavioral symptoms (Sandifer's syndrome), respiratory symptoms (apnea, wheezing, or pneumonia), or failure to thrive. The diagnosis is based on history and questionnaire, barium swallow, endoscopy and biopsy and/or esophageal PH monitoring.<sup>1,2</sup> Treatment in children depends on age and GERD severity and encompasses conservative, pharmacological, and surgical therapy. Pharmacological agents comprise of acid-lowering, barrier, and prokinetic agents.<sup>1-4</sup> Prokinetic agents have tremendous theoretical benefit in reflux, particularly in young children, but that benefit has been challenging to demonstrate objectively, and potential side effects and toxicity have limited their use.<sup>1-2</sup>

Cisapride is a 5-HT<sub>4</sub> agonist, and it was the drug of choice in GERD. It is no longer available in some countries owing concerns regarding prolongation of the Q-Tc interval and cardiac dysrhythmia in childhood.<sup>1,2</sup> In Canada, a survey of use in over 11000 neonates who received cisapride revealed three nonfatal arrhythmias, two with 10-fold dosage errors and one with co-treatment with erythromycin.<sup>5</sup> Different studies were performed regarding to its cardiac effects, they often showed its effect on Q-Tc interval especially in high risk groups such as pre-

mature infants under 3 months age, electrolyte abnormality including hypokalemia and hypocalcemia, cardiac, renal, or hepatic disorders, presence of prolonged Q-Tc interval on ECG, and co treatment with macrolides, imidazoles, or Class III of antiarrhythmic drugs.<sup>6-9</sup>

Extrapyramidal reactions are the most important adverse effect of metoclopramide owing to pass the blood-brain-barrier and block the dopamine receptors in substantia nigra.<sup>1,2</sup> Moreover, there is a report of permanent tardive dyskinesia.<sup>10</sup>

Cisapride effectiveness has been evaluated to 75% according to the literature.<sup>11,12</sup> There is no consensus about efficacy of metoclopramide in pediatric GERD. What's more, some studies have compared efficacy of these two agents in adult age group, and cisapride has showed better efficacy than metoclopramide based on symptom improvement or esophageal PH monitoring criteria.<sup>13-15</sup> Similar surveys were performed in children under 5 years old. These revealed better and faster symptom improvement in children who were treated with cisapride.<sup>16-17</sup>

The current study was performed to determine the efficacy and severe adverse effects of these prokinetic agents in children with GERD.

## MATERIAL AND METHODS

This study was prospective and performed from December 2005 until March 2007, during 15 months, in Children's Hospital Medical Center on 130 children with GERD with age range 1 month to 12 years.

A patient was included in the study if the GERD was confirmed with history and questionnaire, endoscopy, histology, PH monitoring, and/or esophagography. Furthermore, cases with previous antireflux pharmacotherapy were excluded. Cisapride (0.6 mg/kg/day divided in 3 doses in liquid form) was prescribed for the patients as a prokinetic agent except for high-risk patients. This high-risk group was comprised cases with cardiac, renal, or hepatic disease or electrolyte abnormality as well as premature infants

under 3 months age. They were advocated avoiding macrolides or imidazoles as well as class III of antiarrhythmic drugs. If the ECG showed Prolonged Q-Tc interval before treatment, they were excluded from the first group. Thus, metoclopramide(1mg/kg/day in 3 divided dose in drop form ) were given to the high-risk cases. As a result, the patients divided into two groups. The first group was included 104 cases took cisapride, and the rest, 26 cases, were treated with metoclopramide. In addition, if there was any sign of esophagitis in history, endoscopy or histology, patient was given acid-reducing agent. Response was evaluated based on symptom improvement.

ECG was recorded 48- 72 hours after treatment in the first group. Follow-up visits were performed 2,4,8, and 12 weeks after initiation of treatment, and efficacy as well as side effects was assessed. Furthermore, ECG was repeated at the 12th week visits in the first group.

Analysis of data was performed by SPSS software. Moreover, all criteria were carried out with an  $\alpha=0.05$  level of significance.

## FINDINGS

130 patients (1 month- 12 years) were registered for the current study. 104 cases (68 male and 36 female, mean age =14 months with SD=5 months) received cisapride, whereas 26 patients (13 male and 13 female, Mean age =13months with SD=4) were treated with metoclopramide. There wasn't statistical significant difference between two groups in terms of gender and age range distribution.

The patients suffered from regurgitation in 60 cases (50.3% of total cases), poor weight gain 28(21.5%), wheezing 22(13.8%), chronic cough 17(13.7%), abdominal pain 14(10.8%), irritability 11(9.3%), recurrent pneumonia 5 (3.9%), GI bleeding 3(2.3%), and dysphasia, odynophasia, and sandifer's syndrome that each one was 2(1.5%).

From diagnostic point of view, 106 cases underwent barium swallow under fluoro-

scopic examination, and GER confirmed in 101 cases. Additionally, esophageal PH monitoring revealed abnormal reflux index in 9 patients. 92 (96.8%) from 95 cases who were underwent endoscopy had esophagitis evidence, and also biopsy sample showed histologic esophagitis in 96.8%. There were no statistical remarkable differences between two groups in terms of endoscopic or histologic esophagitis and its severity.

In the first group, ECG showed prolonged Q-Tc interval in 10 cases before treatment, thus metoclopramide used instead of cisapride. Q-Tc interval prolongation was observed in 4.8% of cases 48-72 hours after initiation of cisapride, whereas there was no prolonged Q-Tc interval in the 12 week ECG in the rest of the first group. ECG didn't revealed arrhythmia during therapy. The first Q-Tc interval measurements was compared with the second ones based on paired T test, it wasn't remarkably different in terms of statistical view (P Value=0.138). ECG was repeated in the 12 week visit in the first groups. We didn't find any evidence of arrhythmia or Q-Tc prolongation.

## DISCUSSION

GERD is the most common esophageal disorder. Pharmacological agents comprise of acid-lowering, barrier, and prokinetic agents. Prokinetic agents act on regurgitation via their effects on LES pressure, esophageal peristalsis or clearance and /or gastric emptying.<sup>2</sup> These effects have been challenging, and potetial side effects and toxicity have limited their use.

To begin, in this study, we didn't observe any arrhythmia in 104 cases who were treated with cisapride (0.6 mg/kg/day) and didn't have any risk factor, but there was Q-Tc interval prolongation in 4.8% of the patients which wasn't statistically remarkable. On one side, this emphasizes that cardiac effects of this agent is risk factor dependent because the cases in the first group didn't have any risk factor. Various study particularly the Canadian study on 11000 patients proved this result.<sup>5,7,8,9,19</sup> Although some authors stated cisapride doesn't affect Q-Tc

interval in neonate, but we observed Q-Tc prolongation in a few cases. On the other side, it is reasonable that ECG is performed a few days after treatment to find the cardiac effects and to withdraw some cases. Indeed, this measurement lets clinician to recognize the patients who might be susceptible to adverse drug reactions. In addition, the third ECG in this study wasn't demonstrated Q-Tc interval prolongation, so it seems Q-Tc interval didn't increase with continuing therapy in the rest of patients. As a result, two ECG monitoring are necessary and sufficient, one before treatment and another after 2-3 days of initiation of cisapride as long as patients are treated with this dose and don't have any risk factor.

Next, 7.7% of cases that received metoclopramide experienced extrapyramidal reaction. The incidence of severe adverse effects were reported in previous study higher than this study. We don't have clear description for this finding.<sup>2, 13,14</sup>

Last, We couldn't evaluate pure prokinetics efficacy because most of the cases also received acid-lowering agents, but we had opportunity to compare their efficacy based on symptom improvement. The improvement was equal; therefore their effectiveness was assessed similar except in the 12-week visits. At 12-week visits, we observed better symptom improvement in terms of severity, but there was no difference for absence or presence of the symptom between two groups. In fact, the second group felt higher improvement and better quality of life in 12 weeks after treatment. Some authors compared cisapride efficacy with placebo and believed that the significant difference for symptom present/absent and reflux index in esophageal PH monitoring, but not difference for symptom change.<sup>18</sup> Moreover, there are some reports that mentioned better efficacy for cisapride in compare with metoclopramide, but the current study didn't reveal that at least in the first two months of treatment.<sup>13-17</sup> This may have been related to different sample sizes in two groups.

## CONCLUSION

This study demonstrated that cisapride is a safe treatment for GERD considering appropriate cautions. Moreover, we didn't observe better efficacy of cisapride during first two months, but the cases had better quality of life and less symptom severity at 12th week.

## REFERENCES

- Orenstein SR, Khan S, Thomson M. Gastroesophageal Reflux and Esophagitis. In: Walker WA, Sherman PM, Goulet O, et al (editors). *Pediatric Gastrointestinal Disease*. 4th edition. NY: BC Decker Inc. 2004, p: 384-423.
- Vandenplas Y. Gastroesophageal Reflux. In: Wyllie R, Hyams JS, Kay M (editors). *Pediatric Gastrointestinal and Liver Disease*. 3rd edition. Netherlands: Saunders ELSEVIER. 2006, p: 305-323.
- Cezard JP. Managing Gastro-esophageal Reflux Disease in Children. *Digestion* 2004; 69 *Suppl 1*: 3-8.
- Vandenplas Y. Gastroesophageal Reflux: Medical Treatment. *JPGN* September 2005; 41 *Suppl 1*: S41-S42.
- Ward R, Lemons JA, Molteni R. Cisapride: A survey of Frequency of Use and Adverse Events in Premature Newborns. *Pediatrics* 1999; 103: 469-472.
- Zamora SA, Belli DC, Freidli B, et al. 24-hour Electrocardiogram Before and During Cisapride Treatment in Neonates and Infants. *Biol Neonate* 2004; 85(4): 229-236.
- Khorana M, Chankajom W, Kanjanapattanakul W, et al. Effect of Cisapride on Corrected Q-T interval in Neonate. *J Med Assoc Thai* 2003; 86 *Suppl 3*: S590-5
- Levy J, Hayes C, Kern J, et al. Does Cisapride Influence Cardiac Rhythm? Result of United States Multicenter, Double Blind, Placebo-controlled Pediatric Study. *JPGN*, 2001; 32(4): 458-63.
- Benatar A, Feenstra A, Decraene T, et al: Cisapride and Proarrhythmia in Childhood. *Pediatrics* 1999; 103(4 pt 1): 8568-70.
- Putnam D, Orenstein SR, Wessel HB, et al. Tardive Dyskinesia associated with use of metoclopramide in a child. *J Pediatr* 1992; 121: 983-5
- Wiseman LR, Faulds D: Cisapride, Updated Review of Pharmacology and Therapeutic Efficacy as a Prokinetic Agent in Gastrointestinal Disorders. *Drugs* 1994; 47(1): 116-52.
- Mazar LY, Baker RD, Boyel JT: Gastroesophageal Reflux. In: Moyer VA, Ellipt EJ, Devis RL, et al (editors). *Evidence Based Pediatrics and Child health*. 1st edition. London; BMJ Books. 2000, p: 248-63.
- Arabehety JT, Leitano OR, Fasslers S, et al. Cisapride and Metoclopramide in the Treatment of Gastroesophageal reflux. *Clin Ther* 1998; 10(4): 421-8.
- Manousos ON, Apostolos M, Michailidis D. Treat-

- ment of Reflux Symptoms in Esophagities patients: Comparative Trial of Cisapride and Metoclopramide. *Curr Ther Res* 1987; 42: 807-13.
15. Rode H, Studen RJ, Millor AJ, et al. Esophageal PH assessment of Gastroesophageal Reflux in 18 patients and effects of Two Prokinetic Agents: Cisapride and Metoclopramide. *J Pediatr Surg* 1987; 22(10): 931-4.
  16. Gonzalez-Gallicia JA, Juarez G, Galindos, et al. Valoracion Clinica Y Endoscopia de la Eficaci q de Cisapride en Comparacion con Metoclopramidea en el Refluc Gastroesofagio ennios. *Investigation Medica International* 1992; 19: 10-15(Abstract).
  17. Mundo F, Feregrino H, Frenandez J, et al. Clinical Evaluation of gastroesophageal Reflux in Children, A Double Blind Study of Cisapride VS Metoclopramide. *American Journal of Gastroenterology* 1990; 85: 1222(abstract).
  18. Augood C, Maclennm S, Gilbert R, et al. Cisapride treatment for Gastro-oesophageal Reflux in Children. *Cochran database Syst Rev* 2000; (3) CD002300.
  19. Steffen RM. Effects of Cisapride on QT interval in Children. *Clin Pediatr* 1999; 38(2): 121-122.