
CASE-STUDY

THE EFFICACY OF DOMPERIDONE IN THE TREATMENT OF CHILDHOOD GASTROESOPHAGEAL REFLUX DISEASE: REPORT OF 220 CASES

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ABSTRACT

The aim of this study was to investigate the efficacy and side effects of domperidone in childhood gastroesophageal reflux disease. This outcome study was done on 220 children (1month -15years) referred with reflux-related gastrointestinal and extra gastrointestinal symptoms during 3 years. Upper endoscopy with biopsy was performed in all subjects except in infants with apnea. Trial therapy was begun with domperidone (0.6mg/kg/BID) 30 minutes before meal. The efficacy and side effects were evaluated in 4-week follow up. Those free of symptom were considered as positive therapeutic response. In children with esophagitis, omeprazol was prescribed for 3 months too. Follow up continued monthly for three months and then every 3-6 months up to 2 years. Mean age of subjects was 4.99 ± 3.5 years. There was no significant different between two sex (female=55%, male=45%). There was poor correlation between clinical symptoms with endoscopic and histologic findings (100%, 66.4%, 82.7%). Majority of the patients (85.5%) responded to the treatment in 4 weeks. There was no significant relationship between age, sex and clinical symptoms with response to domperidone. Although side effects were observed in 22.4%, but the most frequent side effect (15%) was loose stool. Moreover this complication (constipation) was beneficial in relieving simultaneous reflux related constipation. Serious complications such as extrapyramidal signs were observed only in 0.5%. According to this study, domperidone with few side effects can be efficient for the treatment of reflux in children with any gastrointestinal or extra- gastrointestinal symptom regardless of the sex or age group, moreover further study for finding out rare complications is suggested too.

Keywords: Domperidone/adverse effects, Gastroesophageal Reflux/drug therapy, Child.

INTRODUCTION

Gastrophageal reflux is a relatively common gastrointestinal disorder affecting children. Although self-limited physiologic reflux observed in 20-67% of infants, continuous symptoms after 2 years of age, or severe clinical symptoms at any age requires investigation and intervention.¹⁻³

Diagnosis is often possible based on history and physical examination without any unnecessary expensive investigation.⁴⁻⁶ In the pediatric population, endoscopic visual finding and histologic abnormalities do not always correlate with clinical presentation. Moreover, these findings are not

good predictors of how children will respond to treatment. Gastrophageal reflux may be complicated by esophagitis (61-80%)⁷ in symptomatic children, esophageal stenosis (5%)⁴, growth retardation and respiratory problems, which are indication for treatment. The most widely agents include metoclopramide, cisapride, bethanechol and domperidone are among drugs that have already being used^{7,9}. Some of these drugs such as domperidone and metoclopramide have unknown effects and some like cisapride have to be withdrawn due to its side effects.¹⁴

Unfortunately, there is not agreement on long-term pharmacological therapy for reflux, moreover there is little evidence of efficacy for domperidone. It seems that prokinetic drugs such as domperidone due to increasing lower esophageal sphincter pressure are useful in reflux^{1,8,9}. Although various studies in adults and children were evident the efficacy of this drug with few side effects, its use is controversial^{1,2,8,9}. Metoclopramide and domperidone unlike to bethanechol do not increase gastric acidity¹⁰. Furthermore, metoclopramide dose not seem to be a good choice due to its unknown effects in pediatric reflux and its serious side effects especially in infants (20%)⁷.

Although controversy about the efficacy of domperidone are limited, most of the studies are evident of its relative harmlessness in comparison to other prokinetic agents.^{1,12-14} The side effects include skin rashes, abdominal cramps, loose stool, extrapyramidal reaction, prolactinemia, amenorrhea, genitocystitis and hypertension in patients with pheochromocytoma and rare cases of QT prolongation following intravenous injection of domperidone^{4,7}. In regard to the problems of long-term treatment with domperidone in pediatric reflux and domperidone, we conducted this study to finding out the efficacy and complications of this medication in Iranian children.

Method

This prospective-outcome study was performed on 220 children aged 1 month to 15 years who had referred to the researcher's private office and Afzalipour subspecialty clinic from May 2008 to July 2011. The study protocol was approved by EC.

Symptom profile

The chief complaints of patients were; nausea, vomiting, abdominal pain, dysphagia, regurgitation, sialorrhea, heartburn, cyanosis episodes, apnea, chronic hoarseness (>2 week), chest pain and chronic cough(>2week) resistant to standard treatment. 33 children out of 253 patients were excluded from the study for different reasons.

Inclusion criteria were absence of cardiovascular, hepatic and metabolic disorders, and having symptoms such as dysphagia, heartburn, chronic vomiting or at least three simultaneous complaints of the nonspecific mentioned symptoms.

Esophageal endoscopy

After obtaining parents' consent, children underwent upper endoscopy using pediatric pentax video endoscope (Germany) by pediatric gastroenterologist. At least 2-3 biopsies had taken from the last 5cm of lower esophageal sphincter and the same number from the antral area were collected. Specimens were kept in formalin and transferred to the pathology department of Afzalipour hospital immediately. Upper endoscopy not performed in infants younger than one month with apnea or cyanotic attacks.

Medical therapy and follow up

Trial therapy with domperidone (0.6mg/kg/BID) begun for infants younger than one month for 4 weeks. In other cases, immediately after the endoscopy, domperidone (0.6mg/kg/BID) was administered 30 minutes before meal. Parents were warned about drug side effects such as lethargy, irritability, loose stool, abdominal cramp, skin rashes and extrapyramidal signs, and requested from them to inform the researcher either by phone call or referring in the case of observing any new problems.

All subjects were visited monthly for 3 months. Eighty percent of patients free of symptom after 4 weeks of treatment which was considered as positive response. In cases had esophagitis according to the pathologist report (basal hyperplasia or the presence of less than 20 eosinophils in the high power microscopic field), omeprazole (1-3mg/kg/daily) 30 minutes before breakfast was administered too.

After 3 months of treatment, first omeprazole and then domperidone were gradually withdrawn during a 4 week period and the parents were recommended to refer immediately in the case of symptoms recurrence, and otherwise every 3-6 months. Treatment begun if symptoms recurred again, and domperidone continued every other day in hiatal hernia. Follow up continued by the end of August 2011.

Statistical analysis

Data collection instrument was a questionnaire consisted of age, sex, reason of referring, endoscopic findings, histologic abnormalities, treatment response, side effects of domperidone and outcome (surgery, resolution of symptoms within 4 week, domperidone side effects). The data were analyzed by SPSS17. Continuous unpaired data were

analyzed by using t-test. Categorical variables were analyzed using Chi square test. P values less than 0.05 were considered significant.

Results

Mean age of children was 4.99 ± 3.5 years (1 month-15 years). 26.4% of the subjects were younger than 2 years of age. There was no significant difference between two sex (55% female, 45% male). Most subjects (96%) had been referred with gastrointestinal complaints such as vomiting (bloody or non-bloody), nausea, and abdominal pain (table1).

The most frequent symptom (49.6%) was Vomiting. Hematemesis was observed in 2.3% (table1).

Although endoscopic visual esophagitis and esophageal stenosis were observed in 66.4% and 2.3% respectively, but histological esophagitis was reported in 82.7% of cases.

The majority of patients (85.5%) were responded to domperidone. The side effects were observed in 22.4%. The most common side effect (15%) was loose stool (table2).

There was no significant relationship between treatment response and age ($p=0.662$), sex ($p=0.77$) and type of symptom ($p=0.188$).

Fundoplication was performed in 2.7% of subjects.

Discussion

The results of this prospective study showed that clinical symptoms of reflux have not always good correlation with endoscopic and histologic findings, because endoscopic visual esophagitis and histological esophagitis were observed in 66.4% and 82.7% respectively. This phenomena has been seen in other studies^{1,5,6}. Therefore, it seems that gastroesophageal reflux can be treated based on clinical symptoms without performing unnecessary expensive studies^{1,4,5,6}. In this study, most children (85.5%) were responded to domperidone in 4 weeks. We did not repeat endoscopy and biopsy for the evaluation of treatment response because of poor correlation between clinical symptoms and endoscopic and histologic findings.

Moreover, in some other studies, it has been mentioned that these findings are not good predictors of treatment response.

^{1,5,6}

In De Loore study, response to domperidone has been 75%¹¹ and in another study in California, treatment response has been excellent¹². In one study in London, relief of the most common symptom (vomiting) after treatment with domperidone in comparison to metoclopramide (43%) and placebo (7%) has been significant (75%)¹. In other study

Table1. Clinical parameters of gastro-esophageal reflux in children; Kerman-Iran

Symptom	Number	percent
Vomiting	109	49.6
Abdominal pain	53	24.1
Nausea	40	18.2
Indigestion	5	2.3
Dysphagia	3	1.4
Heartburn	1	0.5
Respiratory problems	4	1.9
Restlessness	2	0.9
Failure to thrive	2	0.9
Sialorrhea	2	0.5
Total	220	100

Table 2. Domperidone side effects in children (n)

Side effect	Number	percent
loos stool	33	15
Restlessness	7	3.2
Abdominal cramp	6	2.7
Skin rashes	1	0.5
Vertigo	1	0.5
Extrapyramidal	1	0.5
Total	49	22.4

clinical response to a prokinetic agent such as domperidone has been 70%¹³. There was no significant relationship between treatment response and variables of age, sex and type of symptom. Lack of significant relationship between positive response and these variables may be evidence of the fact that domperidone is well tolerated in all age groups with any reflux related symptoms (gastrointestinal, extra-gastrointestinal) in both sex. According to some studies, domperidone is well tolerated and harmless^{13,14}, while some others were reported serious complications¹.

Although, in this study, domperidone side effects were seen in 22.4%, but the most frequent side effect (15%) was loos stool. This complication was beneficial for simultaneous reflux associated constipation.

Serious complications such as extrapyramidal were observed in just 0.5% of cases. This figure in comparison to the high serious side effects of metoclopramide and cisapride is not significant^{1,7,8}. It should be mentioned that in the present study complications such as genicostomy, QT prolongation and hyperprolactinemia have not been studied.

According to this study, domperidone is an useful prokinetic agent with few side effects in all age groups of children. Although, trial therapy for 4 week is recommended with evaluation of clinical improvement, further study for rare complications is suggested too.

REFERENCES

1. Pritchard DS, Baber N, Stephenson T. Should domperidone be used for the treatment of gastroesophageal reflux in children? Systematic review of randomized controlled trial in children age 1 month to 11 years old. *Br J Clin Pharmacol* 2005; 59(6):725-729.

2. Nelson SP, Chen EH, Syniar GM, Christoffel K. Prevalence of symptoms of gastroesophageal reflux during infancy: a paediatric practice-based survey. *Arch Pediatr Adolesc Med* 1997; 151: 569-72.
3. Kliegman RM, Stanton BF, St. Geme JW, et al. (eds) *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia, PA: Saunders Elsevier; 2011.
4. Vieira MC, Miyague NI, Van Steen K, et al. Effects of domperidone on QTc interval in infants. *Acta Paediatr*. 2012;101(5):494-6.
5. Bnhamou P, Candramel S, Cezard JP, Cucchiara S, et al. Current concepts and issues in the management of regurgitation in infants. *Acta Paediatrica* 1996; 85:531-4.
6. MacLennan S, Augood C, Cash-Gibson L, et al. Cisapride treatment for gastroesophageal reflux in children. *Cochrane Database Syst Rev*. 2010;14(4):CD002300.
7. *Gastroesophageal reflux disease & Esophagitis*: Robert Wyllie, Jeffrey S Hymas, *Pediatric Gastrointestinal and liver Disease*, 3th ed, 2006: Pp 305,316.
8. Ramirez B, Richter JE. Review article: Proton pump inhibitors in the treatment of gastroesophageal reflux disease. *Aliment Pharmacol Ther* 1993; 7(1):5-20.
9. Tytgat GN, Nio CY. The medical therapy of reflux oesophagitis. *Baillieres Clin Gastrentrol* 1987; (4): 791-807.
10. Barone JA. *Ann Pharmacother*. Domperidone: a peripherally acting dopamine2-receptor antagonist. 1999; 33(4):429-40.
11. De Loore L, Van Ravensteyn H, Kleingman R, Winter H. Domperidone drops in the symptomatic treatment of chronic pediatric vomiting and regurgitation. A comparison with metoclopramide. *Postgrad Med J* 1979; 55: 40-2.
12. Bruce B, Grill, Craig Hillemeier, Lucille A, Semararo, et al. Effect of domperidone therapy on symptoms and upper gastrointestinal motility in infants with gastroesophageal reflux. *The Journal of Pediatrics* 1985;106: 311-16.
13. Matias E, Manzotti, Hgo N, Catalano, Fernando A, Serrano, Gisela DI, Stilio, et al. Prokinetic drug utility in the treatment of gastroesophageal reflux esophagitis: a systematic review of randomized controlled trials. *Open Medicine* 2007; 2007;1(3):e171-80.
14. Bines JE, Quinlan JE, Treves S, Kleinman RE, et al. Efficacy of domperidone in infants and children with gastroesophageal reflux. *J Pediatr Gastro Nutr* 1992; 14 (4):400-5.