



ORIGINAL ARTICLE

Effects of cisapride and chest physical therapy on the gastroesophageal reflux of wheezing babies based on scintigraphy

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Abstract

Objective: to evaluate the effect of cisapride and chest physical therapy on the gastroesophageal reflux of wheezing babies.

Methods: we prospectively assessed the presence of technetium (99Tc) in the upper, middle, and lower esophagus of 25 wheezing babies (13 with GERD and 12 without GERD) using scintigraphy. Both groups underwent clinical investigation, including laboratory, X-ray and scintigraphy tests, for the etiology of the wheezing baby syndrome (WBS) and GERD. Expiratory Flow Acceleration (EFA) was performed before and after treatment with cisapride. The total time of GER episodes was accounted for each portion of the esophagus during scintigraphy and during EFA.

Results: cisapride significantly reduced the total reflux time in the upper esophagus ($P<0.05$), but showed no influence during EFA. After cisapride therapy, EFA increased the total reflux time in the upper and medium esophagus; however, no statistical significance was found. Infants with GERD presented a shorter total reflux time in the distal esophagus ($P<0.05$) during EFA. After cisapride treatment, no statistical significance was found. Infants without GERD also presented reduced total reflux time in the distal esophagus during EFA ($P<0.05$). Those with GERD had increased total reflux time in the distal esophagus ($P<0.05$) before and after cisapride treatment during EFA and scintigraphy.

Conclusions: cisapride was effective in reducing the total reflux time, mainly in the upper esophagus. EFA apparently increased the number of episodes of GER, without achieving statistical significance. Further studies are necessary to investigate the effects of chest physical therapy according to body positions.

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Introduction

Recent data¹ indicate that up to 25% of infants present recurrent wheezing, thus constituting a large number of pediatric patients.² There are several mechanisms and characteristics that constitute risk factors for wheezing in infants, including flaccidity and small caliber airways,

bronchospasms, accumulation of secretion, and inflammation. Diseases most frequently related to wheezing are atopy, viral infection, gastroesophageal reflux disease (GERD), and, in some cases, presence of foreign body or extrinsic airway compression.^{1,2} The clinical manifestation of Wheezy Baby Syndrome (WBS) is persistent or recurrent wheezing, and it reflects obstruction of the airways.

Gastroesophageal reflux (GER) is the involuntary return of gastric content to the esophagus with or without regurgitation or vomit of saliva, food, and gastric, bile and/or pancreatic secretion.³⁻⁷ GER can be physiological and the term gastroesophageal reflux diseases (GERD) is used to describe the wide range of disorders caused by GER.³ The distinction between physiological GER and GERD is based on the amount of GER; in this sense, GERD is characterized by increased frequency, intensity, and duration of GER episodes and by damage to esophageal mucosa and/or respiratory tract. GER is the disorder that most commonly affects the lower esophageal sphincter (LES) and it should be considered a cause for intractable respiratory diseases, including wheezing.^{6,8}

The relation between WBS and GER is complex and controversial.³⁻⁵ The higher prevalence of GERD in wheezy babies does not indicate, by itself, a causal relationship between the two. GERD can cause or deteriorate situations of bronchial obstruction due to aspiration, vagal reflex, increase in bronchial responsiveness, and release of tachykinins. Altered pulmonary mechanics in wheezy babies (cough, increase in transdiaphragmatic pressure gradient, diaphragmatic adjustment due to overinsufflation) and use of refluxogenic medication (methylxanthines and systemic sympathomimetics) are risk factors for GERD.^{5,9}

The diagnosis of GERD should be confirmed by at least two diagnostic methods, including radiological, scintigraphic, or ultrasonographic studies.¹⁰⁻¹² This criterion of two methods should be adopted in cases where it is not possible to carry out prolonged esophageal pH monitoring, the diagnostic method of choice for GERD.¹³

Treatment of GERD involves clinical (elevated positioning, diet, and pharmacotherapy) and surgical measures,^{6,14} and its objective is of reducing aggressive factors of GERD and increasing protective factors of the esophageal mucosa.¹³⁻¹⁷ Included in the group of medications for treatment of GERD, there is the cisapride (cis-4-amino-5-chloro-N[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide monohydrate), whose main mechanism of action is considered to be the stimulation of myenteric cholinergic nerves with consequent increase of acetylcholine release.^{18,19} The anti-GER effect of cisapride is a result of esophagus and stomach muscle contraction and LES tonus for coordination of antropyloroduodenal motility, thus accelerating emptying, and hindering stasis, of gastric content.^{15,18} The medication does not affect gastric secretion, does not stimulate dopaminergic receptors, and

has no central nervous system side effects.^{20,21} Despite recent questioning on the safety of cisapride, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition⁹ recommends use of the medication with the exception of patients who present arrhythmia, hydroelectrolytic disorders, hepatic insufficiency, or who are being administered drugs that interfere with the P450 cytochrome, such as the antifungal azoles (ketoconazole, myconazole, and itraconazole) and the macrolide antibiotics (erythromycin, clarithromycin, and troleandomycin).^{4,7,8,13,19,22}

Many children who develop wheezing and airway obstruction due to bronchial hypersecretion are frequently indicated to the Chest physical therapy Department of the Hospital de Clínicas, teaching hospital of the Universidade de Campinas (UNICAMP). The objective of chest physical therapy is increasing mucociliary clearance, clearing obstructed airways, and improving ventilation and gas exchange.²³ Chest physical therapy is a complementary therapy for atelectasis, bronchiectasis, and breathing disorders deteriorated by excess and/or retention of bronchial and pulmonary secretion (cystic fibrosis, WBS, and chronic bronchitis).²⁴⁻²⁶

However, we observed that there are few studies in the literature regarding risks and benefits of chest physical therapy for WBS; we also observed that there is a lack of standardization of physical therapy procedures for the treatment of wheezy babies with or without GERD. Our objective was to analyze the effect of cisapride and chest physical therapy on GER of patients with WBS.

Patients and methods

We selected atopic wheezy babies (WB) registered at the Allergy-Immunology and Pediatric Pneumology outpatient clinic of the Hospital de Clínicas, UNICAMP. Criteria for inclusion of infants in the population were age older than three months and at least three wheezing episodes or one episode of persistent wheezing for over 30 days.² Diagnosis of atopy was established according to patient clinical history, serum IgE levels above the 95th percentile for patient age, hemogram finding of 5% or more eosinophils, and family history of atopy (father or mother).²⁷ Informed consent was obtained from all parents and guardians of infants. Our study was approved by the Ethics Research Committee of the School of Medicine, UNICAMP.

Patients were analyzed prospectively and divided into two groups. The first group included atopic infants with GERD confirmed by X-ray of the esophagus, stomach, and duodenum after barium, and by scintigraphy for GER indicating episodes on distal, mid, and upper segments of the esophagus. Group 1 patients received cisapride for four to eight months (average of six months) 3 times daily and at 0.2 mg/kg/dose. The second group included atopic WB who

presented negative or rare X-ray and scintigraphic findings of GER into the distal esophagus; these patients, thus, were not considered carriers of GERD. Both groups were submitted to clinical, laboratory, radiological, and scintigraphic examinations for etiological investigation of WBS; these examinations were carried out according to routine procedures of the Allergy-Immunology and Pediatric Pneumology services, including hemogram, serum hemoglobin levels (IgA, IgG, IgM, IgE), Mantoux test, and sodium and chlorine levels in sweat.

We excluded WB with contraindication for use of cisapride⁷ or with malnutrition, low height or weight for age, congenital infections, tuberculosis, cystic fibrosis, cardiopathies, genetic diseases, delayed neuropsychomotor development, primary or secondary immunodeficiency, or other well-known chronic diseases. We also excluded infants who presented with situations that present contraindication for physical therapy such as pneumothorax, pneumatocele, pleural effusion, acute respiratory failure, and lung abscess. The use of inhaled beta-agonists was allowed during bronchial obstruction attacks. No patient was using inhaled beta-agonists during the week in which scintigraphic studies were carried out. Patients who presented attacks and required systemic corticosteroids or bronchodilators were excluded from the study.

Radiological study

The radiological study was carried out following the criteria of McCauley *et al.*,²⁸ which were adapted by the Department of Radiology at the School of Medicine, UNICAMP. After a four-hour fasting period, WB were administered barium solution enough to fill the stomach. Next, these patients were examined by intermittent fluoroscopy for five minutes which allowed for important x-ray images. Patients were examined in supine position with emphasis on anatomy and functioning of the esophagus; patients were examined in right lateral decubitus with emphasis on anatomy and functioning of the esophagus and duodenum. In the radiological studies, we observed esophageal clearance and topography affected by GER episodes for classification into grade 1 (reflux into the distal esophagus only), grade 2 (into the mid-esophagus), and grade 3 (into the upper esophagus) episodes.

Scintigraphic study

Scintigraphic exams were carried out at the Nuclear Medicine Services of the Hospital de Clínicas at the School of Medicine, UNICAMP. Exams were carried out in two stages: first, a baseline study and, second, chest physical therapy study. After a six-hour fasting period, each infant was given the test meal with 18.5 MBq (0.5 mCi) of Tc-99m sulfur colloid, added to the volume of milk that babies normally ingested and using their own bottles. Patients were positioned in supine horizontal with collimator onto the upper thorax and upper third portion of the abdomen. We

used a low-energy collimator with high sensitivity. During baseline scintigraphic examination, we acquired images at every two seconds for 15 minutes. Next, during chest physical therapy, we again acquired images at every two seconds for 15 minutes.

GER episodes were assessed according to topography of the esophagus (reflux into distal, mid, or upper esophagus) and to duration of episodes in seconds. First, we assessed RGE episodes during baseline scintigraphic examination and, second, during chest physical therapy. Images acquired during both examinations were stored into a computer and analyzed separately. Total duration of GER episodes (TGER) was calculated according to distal, mid, and upper segments of the esophagus. TGER results were expressed in seconds of observed GER for each patient. Examination for lung aspiration was carried out four and 24 hours after the beginning of the study.

Chest physical therapy

We employed a technique of acceleration of expiratory flow (AEF) with passive maneuvers; in other words, without voluntary cooperation of the infant. This technique was employed with the objective of increasing duration and velocity of expiratory flow; it employs two different velocity and flow modalities: slow and rapid AEF.²⁹ The technique was carried out for 15 consecutive minutes after baseline scintigraphic examination. Patients were submitted to synchronized thoracic movement at the beginning of the inspiratory plateau; physiological expiratory limits of children were observed. The velocity of induced airflow is higher than that of normal expiration and is near that of cough; in this sense, AEF allows for possible normal lung physiology by means of airflow variations aiming at bronchial clearance and uniform pulmonary ventilation.³⁰ The physical therapist positioned one hand on the thorax (expiratory pressure hand) and the other on the lower rib cage, thus minimizing increase in abdominal pressure and, consequently, iatrogenic GER episodes. Despite the fact that this technique allows for the use of several positions, patients were only positioned supine, which is the routine position used in baseline scintigraphy and physical therapy procedures.^{29,30}

Statistical analysis

TGER values were collected in relation to distal, mid, and upper esophagus segments and from each infant. Statistical analyses were carried out according to WB with or without GERD; to GER into distal, mid, or upper esophagus; to administration of cisapride; and to chest physical therapy. Following a descriptive statistical analysis, TGER values were compared using the Wilcoxon or Mann-Whitney nonparametric tests for a significance level of $P < 0.05$.³¹

Results

Patients

The first group of patients included 13 atopic WB (10 boys, 3 girls) with age average of 9.8 months and weight average of 11.6 kg; all 13 patients had GERD confirmed by X-ray of the esophagus, stomach, and duodenum after barium and by scintigraphic examination for GER with episodes into the distal, mid, and upper esophagus. The second group of patients included 12 atopic WB (6 boys, 6 girls) with age average of 8.7 months and weight average of 10.7 kg; all 12 patients had negative (or rare into the distal esophagus) GER episodes according to X-ray and scintigraphic examinations. Thus, these patients were not diagnosed with GERD. Both groups were similar as to severity of WBS with sporadic use of short-term, inhaled bronchodilators.

Study protocol

During baseline scintigraphic examinations, we observed that, following cisapride treatment, there was a decrease in TGER in wheezy babies with GERD and according to all three esophageal segments. This decrease was statistically significant only in relation to the upper esophagus (Figure 1; $P < 0.05$; $n = 13$; Wilcoxon test). During chest physical therapy, we observed that cisapride treatment did not influence TGER in any of the segments of the esophagus (Figure 1; $P > 0.05$ in all cases; $n = 13$; Wilcoxon test).

Before treatment with cisapride, we observed that GERD wheezy babies presented lower TGER into the distal and mid esophagus and during chest physical therapy, which was carried out after baseline scintigraphy. These lower values were statistically significant only in relation to TGER into the distal esophagus (Figure 1; $P < 0.05$; $n = 13$; Wilcoxon test). Conversely, we observed that wheezy babies with GERD, when treated with cisapride, presented a trend of increase in TGER into the mid and upper esophagus; however, this increase was not statistically significant (Figure 1; $P > 0.05$ in all cases; $n = 13$; Wilcoxon test). These results seemed rather contradictory since the literature considers that chest physical therapy is a refluxogenic factor, and treatment with cisapride a means of control.

In order to clarify this apparent contradiction, we confronted the results of the GERD wheezy babies before and after cisapride treatment, and recorded during baseline scintigraphy or chest physical therapy, with those of the no GERD wheezy babies, thus without cisapride treatment, and recorded during baseline scintigraphy or chest physical therapy. The wheezy babies with no GERD also presented lower TGER into the distal esophagus during chest physical therapy, which was carried out after the 15-minute baseline scintigraphy procedures (Figure 2; $P < 0.05$; $n = 12$; Wilcoxon test). Before cisapride, we observed that TGER into distal

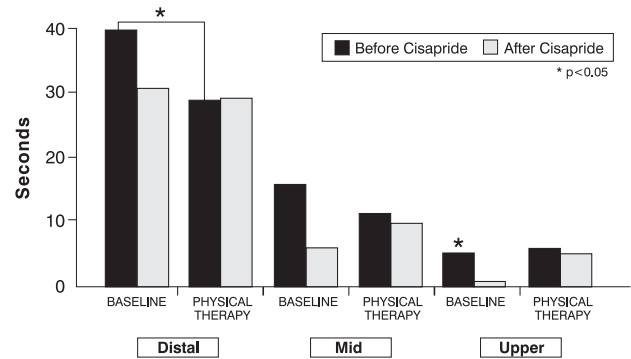


Figure 1 - Average total duration of GER episodes (TGER) in the upper, mid, and distal esophagus according to scintigraphic findings in wheezy babies with gastroesophageal reflux disease (GERD) before and after cisapride therapy, during baseline scintigraphy, and chest physical therapy, using the technique of expiratory flow acceleration

esophagus of GERD wheezy babies ($n = 13$) was significantly higher than that of no GERD wheezy babies ($n = 12$), during baseline scintigraphy or chest physical therapy (Figure 2; $P < 0.05$; Mann-Whitney). Even after cisapride, we observed that TGER into distal esophagus of GERD wheezy babies ($n = 13$) remained significantly higher than that of no GERD wheezy babies ($n = 12$) during baseline scintigraphy or chest physical therapy (Figure 2; $P < 0.05$; Mann-Whitney).

Discussion

GER is the most important disorder of the esophagus and LES in childhood. It is considered a risk factor for recurrent respiratory infections, asthma attacks, and deterioration of the condition of patients with chronic pneumopathy. It is the most widely sought for disorder in differential or associated diagnosis in wheezy babies; in this sense, investigation for GER is mandatory at our services.³ We used a definition of WBS² that is similar to that reported by other authors;^{18,32-36} this definition was chosen since it is the most widely referred to and accepted definition in the Brazilian literature.

In the population of 25 atopic wheezy babies (13 GERD and 12 no GERD), we observed a prevalence of boys (64%), which is in agreement with the literature.¹ There are few studies comparing race and age at onset and severity in wheezy babies. Despite the fact that there are classifications of phenotypes of wheezy babies for patients aged older or younger than three years,¹ there are no studies regarding wheezing in patients aged younger than three years, with the exception of differential diagnosis. Our population presented uniform clinical characteristics of atopic, wheezy babies

who presented different RGE manifestations according to two types of exams.

Assessment of results (Figures 1 and 2) suggests that TGER into the different segments of the esophagus is inversely proportional to the distance from the LES in all situations studied (pre- and posttreatment with cisapride; during baseline scintigraphy or chest physical therapy). This finding is still not fully understood in relation GER pathogeny; even pH-monitoring studies have not been able to explain what is more pathogenic: several GER episodes into the distal esophagus or few episodes into the proximal esophagus.¹⁵

Prokinetic agents such as cisapride speed up gastric emptying and, thus, minimize the risk for GER episodes.¹⁵ Our results indicate that cisapride decreased TGER in all segments of the esophagus of wheezy babies with GERD; these results, however, were statistically significant only for the upper esophagus (Figure 1). These findings indicated a new particularity of the medication, which is that of decrease in GER episodes into the upper esophagus, which are responsible for mechanisms of wheezing secondary to aspiration.⁴

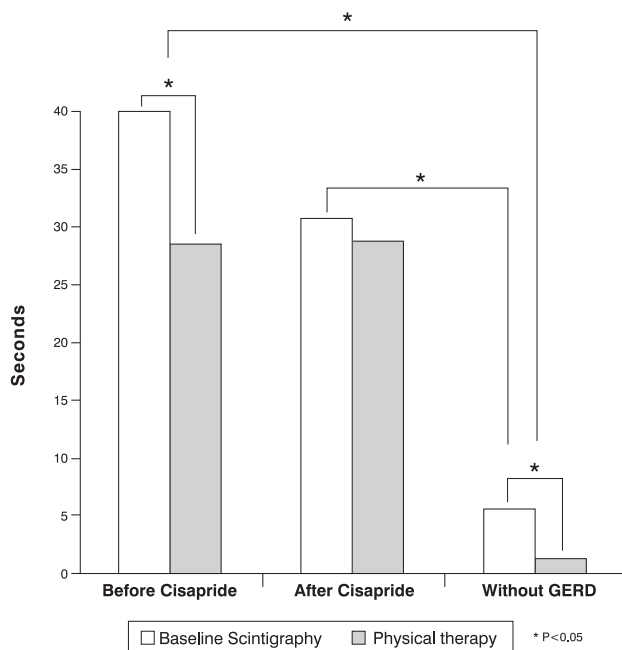


Figure 2 - Average total duration of GER episodes (TGER) in the distal esophagus according to scintigraphic findings in wheezy babies with or without gastroesophageal reflux disease (GERD) before and after cisapride therapy, during baseline scintigraphy, and chest physical therapy, using the technique of expiratory flow acceleration

Conversely, during chest physical therapy, which was carried out 15 minutes after baseline scintigraphy, treatment with cisapride did not influence TGER in GERD wheezy babies into any of the three segments of the esophagus (Figure 1). This suggests that physical stimulation may have a refluxogenic effect that is not antagonized by cisapride. We emphasize that the mechanisms that regulate LES tonus depend on opening and closing strength of the sphincter.³⁷ Though the mechanisms through which chest physical therapy influences function of LES are still not well understood, we find it interesting that physical therapy can antagonize the most potent prokinetic drug used in pediatrics.

Despite the fact that cisapride is an effective prokinetic agent for the treatment of GER,⁷ our data indicate that even after cisapride treatment, GERD wheezy babies presented TGER significantly higher in the distal esophagus, in comparison to no GERD wheezy babies (Figure 2). This finding indicates that, in wheezy babies with GERD, cisapride did not establish the same pattern for GER into the distal esophagus of wheezy babies without GERD.

During chest physical therapy in wheezy babies with GERD, before the treatment with cisapride, we observed a significant decrease in TGER into the distal esophagus following partial gastric emptying ($P < 0.05$); this decrease in TGER was not observed into the mid and upper esophagus. It is possible that chest physical therapy is of little importance to GER episodes into the distal esophagus, as indicated in Figure 1 where the therapeutic stimulation increased TGER into the mid and upper esophagus even after cisapride.

Classical chest physical therapy consists of physical stimulation to the chest region and of postural drainage to assist in the removal of tenacious bronchial secretions.^{25,26,38} Vandenplas et al.³⁹ while using conventional chest physical therapy techniques such as postural drainage in the Trendelenburg position, percussion, vibration, and provoked coughing, observed episodes of GER in three different groups of infants: with GER, with acute respiratory disease, and controls. There was no evidence of a temporal correlation between provoked coughing during physiotherapy and episodes of gastro-oesophageal reflux; the role of position was not examined.

Posture is known to have a substantial impact on the frequency of transient lower esophageal sphincter relaxations. These relaxations, rather than low basal sphincter pressure or increased intragastric pressure are thought to be the predominant mechanism of increased gastroesophageal reflux in patients who develop esophagitis.⁴⁰ Posture is a constant concern for bronchial clearance of GER infants.³⁸ Some authors do not recommend postural drainage in GER patients and indicate supine with 30 degrees head up tilt as an essential part of nonmedication treatment.^{6,13} Different studies present controversial conclusions as to use of Trendelenburg position for bronchial clearance in GER patients.^{41,42} Conversely to Vandenplas et al.,³⁹ we did not

perform maneuvers of abdominal compression to provoke coughing, and we did not observe an increase in GER in wheezy babies without GERD.

AEF allows for positive clinical results when applied to wheezy babies with bronchial hypersecretion. This technique is carried out with use of the hands and can control stimulation, velocity of airflow, and duration of the expiratory period; the technique can be adapted according to need for motility of secretions in either central or peripheral airways. Stimulation should be carried out according to chest size of the pediatric patient.^{29,30} In our study, in order to maintain quality of the technique, AEF was always carried out by the same professional.

As in any other clearance maneuver for infants, AEF can increase negative intrathoracic pressure since, often times, it increases inspiration and cough, and provokes crying. This stimulation did not provoke lung aspiration in any of the infants studied, even in those positioned supine and in postprandial period - finding that corroborates the safety of the technique. However, further studies should be carried out in order to assess efficacy of AEF in comparison to conventional techniques.

GER episodes, to a certain extent, are a normal phenomenon in infants aged younger than one year. These babies can present reflux up to two hours after meals.⁴³ Considering that scintigraphy is a postprandial test, it can detect both physiologic and pathologic GER; this may lead to difficulties in indication of treatment without the corroboration of other diagnostic methods. In our study, GER was diagnosed according to X-ray and scintigraphy findings. Despite the fact that postprandial GER can occur in healthy subjects, it can also cause severe lung disease⁴ and life-threatening events.^{10,13,45} Others have emphasized that episodes of massive aspiration can occur during the postprandial period, thus refuting the understanding that postprandial GER is always physiologic.^{32,46}

Scintigraphy can be carried out for prolonged periods of time without increasing exposure of patients to radiation; these examinations are noninvasive;^{47,48} do not require sedation;⁴⁹ are well-tolerated; and fast.³⁵ Moreover, they allow for recording lung aspiration,⁵⁰ determine characteristics of GER such as volume, clearance, and duration,⁵⁰⁻⁵² and, consequently, assess the effects of prokinetic drugs in the treatment of GER.⁵¹ Latini *et al.*⁵² indicated that scintigraphy can be considered effective and reliable for diagnosis of GER.

Some authors^{44,51-23} consider that scintigraphy is superior to pH monitoring for the diagnosis of GER; whereas others consider the exact opposite.^{3,54} Vandenplas *et al.* suggested that these two procedures explore different conditions and are both useful in the investigation of GER in infants.⁵⁵ These controversies can be explained by the variation in standardization of these techniques. Shay *et al.*⁴¹ and Vandenplas *et al.*⁵⁵ compared the two techniques

during the postprandial period; findings indicated higher sensitivity of scintigraphy in the detection of postprandial GER. This is explained by the fact that the stomach is distended and its pH is neutralized by the ingested meal; thus, the GER is detected by scintigraphy but not by pH monitoring, which cannot detect neutral pH GER episodes. In this sense, scintigraphy does not depend on gastric content pH to detect GER.

WBS and GER are still two of the most important entities and they present several questions that need to be answered. The cause and effect relationship between WBS and GER is still controversial, thus indicating the need for further studies on the mechanisms involved. We concluded that cisapride was effective in decreasing TGER, especially into the upper esophagus of wheezy babies with GERD, and that AFE apparently increases the number of GER episodes, though without causing lung aspiration or other clinical effects.

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