

A pilot trial on the treatment of gastroesophageal reflux-related cough in infants

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Background: Diagnosing asthma in infancy is largely made on the basis of the symptoms of cough and wheeze. A similar presentation can be seen in neurologically normal infants with excessive gastroesophageal reflux (GER). There are no randomized placebo controlled studies in infants using proton pump inhibitors (PPI) alone or in addition to prokinetic agents.

Objectives: The primary objective was to confirm the presence of excessive GER in a population of infants that also had respiratory symptoms suggestive of asthma. Second, in a randomized placebo-controlled fashion, we determined whether treatment of GER with bethanacol and omeprazole could improve these respiratory symptoms.

Methods: Infants (n=22) with a history of chronic cough and wheeze were enrolled, if they had evidence of GER by history and an abnormal pH probe or gastric emptying scan. Infants were randomly allocated to four treatment groups: placebo/placebo (PP), omeprazole plus bethanacol (OB), omeprazole/placebo (OP), bethanacol/placebo (BP). Evaluations by clinic questionnaire and exam, home diary, and pH probe data were done before, after study-medication and after open label of OB.

Results: Nineteen children were studied. PP did not affect GER or respiratory symptoms, and did not decrease GER measured by pH probe. In contrast, OB decreased GER as measured by pH probe indices and parental assessment. In association, OB significantly decreased daytime coughing and improved respiratory scores. No adverse effects were reported.

Conclusions: In infants with a clinical presentation suggestive of chronic GER-related cough, the use of omeprazole and bethanacol appears to be viable therapeutic option.

Keywords: Cough; gastroesophageal reflux; pediatric asthma; esophagus

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Introduction

Diagnosing asthma in infancy is a difficult process compared to that in older children or adults. Often the diagnosis of asthma is made on the basis of the symptoms of cough and wheeze alone.

Even in neurologically normal infants, a similar presentation of chronic cough, increased respiratory effort, and wheezing can be secondary to excessive gastroesophageal reflux (GER) (1-3). It is unclear whether this is due to aspiration

of gastric contents into the airway, to contact of acid on or around the larynx, or from reflexes in the esophagus (2). While GER is a more common event at this age (4), some infants can still have GER more frequently and/or of larger volumes than other babies such that it may cause pathology. Gastroesophageal Reflux Disease (GERD) is defined as esophageal disease as a result of excessive GER (4,5), and studies regarding management of GERD in infants are approached from a this perspective focusing on esophageal

pathology (4). Most gastroenterologists would not call GER a disease without evidence of esophageal pathology. Unfortunately, the respiratory pathology from GER does not usually fit in this definition. The issue of GER and secondary lung pathology has been examined in many studies, but consensus regarding the correct management for infants with excessive GER and lung disease remains unclear.

Gastric motility is a complex motor action of the stomach. Some infants with abnormal GER have a decreased rate of gastric emptying. Gastrointestinal (GI) prokinetic agents could improve gastric emptying decreasing available gastric residue to reflux. Acid suppressing and prokinetic GI drugs are used in children with recurrent pulmonary disorders, including wheezing, cough, and frank aspiration with the expectation that use of these drugs would decrease GER and pulmonary disease. There is reliable evidence in children to support both acid suppressing drugs and prokinetic agents *i.v* to decrease volume and acidity of gastric contents pre-operatively (6-8). There is only one study to support their use in infants with associated lung disease using the prokinetic agent, cisapride, and the H₂ blocker, ranitidine (9). The motility agent cisapride has been completely removed from today's market secondary to unacceptable cardiac side effects versus benefits (10), and there are newer and better acid blockers approved for pediatrics, the proton pump inhibitors.

Overall, no study with proton pump inhibitors alone or in addition to prokinetic agents has been done in a randomized placebo-controlled fashion to show an effect on GER-related respiratory symptoms. Bethanacol (Urecholine®) is a parasympathomimetic agent, which stimulates gastric motility, increases gastric tone, and affects motility (11). Omeprazole (Losec®) is established in pediatrics for its ability in reducing stomach acidity (12). We hypothesized that many infants presenting with asthma-like symptoms have excessive GER as a primary etiology. This study was designed to confirm the presence of excessive GER in a population of infants with the respiratory symptoms of asthma. Second, in a randomized placebo-controlled fashion, we determined whether treatment of these infants with bethanacol and omeprazole could improve respiratory symptoms.

Methods

Study entry criteria

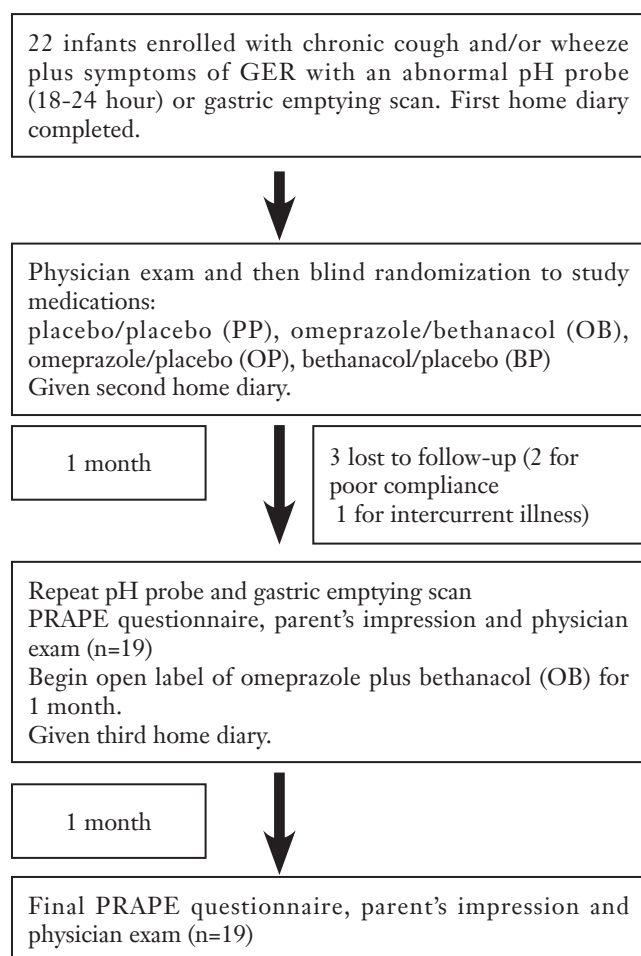
Infants (3 months -2 years) were recruited in Pediatric Pulmonary and Gastroenterology clinics (Stollery Children's Hospital, University of Alberta). All people have

gastroesophageal reflux (GER) events. Gastroesophageal Reflux Disease (GERD) is defined as confirmed esophageal disease because of excessive GER. Most gastroenterologists would not call GER a disease without evidence of esophageal pathology. Unfortunately, the respiratory pathology from excessive GER does not usually fit in this definition. For our study, infants were enrolled if they were affected by chronic (>3 months) respiratory disease (recurrent cough and/or wheeze), daily GER symptoms (visible emesis and/or rumination), and objective evidence of abnormal GI motility (either an abnormal pH probe or significantly delayed gastric emptying on a nuclear medicine scan). Dual channel pH probes were placed for an 18-24 hour period (GERD Chek, Sandhill, Denver CO). While infants are more likely to also have non-acid events, unfortunately esophageal impedance measurements were not available in our centre for this study. Gastric emptying scans were performed using technetium labeled infant formula, taking one-minute images over 120 minutes to calculate an emptying half time. While there are no accepted normative guidelines available for infants, based on available childhood and adult literature (13,14) and our radiologists' experience, most infants should have emptying times less than 90 minutes. An abnormal scan was defined as an emptying half-time greater than 90 minutes. Respiratory and GER symptoms were not necessarily temporally related for inclusion as this was not possible. Consent for a repeat pH probe and gastric emptying scan was required. Infants were excluded if they were allergic to any study medications, if they had known anatomic or neurological factors predisposing to direct pulmonary aspiration (*i.e.* tracheostomy, laryngeal cleft, cerebral palsy), if they had food refusal or failure to thrive, or if caregivers were unable to reliably follow the directions of the study. All parents gave written informed consent as approved by the Health Research Ethics Board, University of Alberta, prior to entry.

Study design

Infants were blindly coded and allocated to one of four study-medication protocols: placebo/placebo (PP), omeprazole/bethanacol (OB), omeprazole/placebo (OP), bethanacol/placebo (BP). Patient allocation and recording of drug-related data was performed blindly in the pharmacy research unit. Based on published data, omeprazole MUPS tabs (10 mg) were given to parents to be dissolved in water or juice based on a dosing guideline of 1/2 tab BID for infants 5-7.5 kg, 1 tab BID for 7.5-12.5 kg, 1.5 tab BID for

Study flowchart

**Figure 1** Test process.

=12.5-17.5, >17.5 kg received one 20 mg tab (approximately 1 mg/kg/dose). Lactulose in a tablet served as placebo. Bethanacol was dissolved in oro-plus and ora-sweet in a 1:1 ratio, and this vehicle was also used as placebo (15). After one month, infants were restudied with pH probe and nuclear medicine gastric emptying scan. Infants continued on open label therapy, of omeprazole plus bethanacol for another month. CONSORT guidelines were followed for preparation of this manuscript (*Figure 1*).

Study outcome data

Before each visit, infants were assessed by a caregiver diary to record respiratory and GER events in the previous 7 days, including: number/day of coughing spells (not during feeds); coughing spells at night; wheezing spells; episodes

of emesis/rumination; fever; and apnea. The values were averaged for the week as events/day. Emesis was defined as visible stomach contents in the mouth, while rumination was defined as the parent's impression of stomach contents coming up but being swallowed down without visualization in the mouth. A Potential Reflux Associated Pulmonary Event (PRAPE) questionnaire covering similar data was completed at each visit with the parent. The parent diary was used to help parents recall their child's past week of symptoms to generate more accurate data regarding the respiratory and GER data. Parents were also questioned regarding the use of asthma medications during the study month (less often, same, more often). At each visit, both parent and doctor gave their impression of the response to therapy. Physicians were blinded to parent's impression. Impression was graded as: worse (−1), same (0), better (+1), and much better (+2). To objectively grade changes in pulmonary health, physicians used a standardized respiratory scoring sheet adapted from a study on infant respiratory distress (16). Infants were graded (0-4 with 4 being the most severe) for respiratory rate, wheezing, crackles, and chest retractions for a total score out of 12. Combined total score was recorded pre-study, post study and post open label. pH probe results pre and post study-medication were scored in a blinded fashion for percent time with pH<4.0 (RI%), number of episodes with pH<4.0, and a combined score. Scores were measured using the DeMeester method (17,18). Gastric emptying scans were also compared pre and post the study drug period. An abnormal scan was based on significant delays in gastric emptying time.

Statistical analysis

During preparation of this study, there were no studies in infants with this clinical scenario using a scoring system similar to ours. Thus, we based power calculations on published pH probe data and the assumption that therapy would have a strong impact on respiratory symptom scores. We planned for 40 infants total, but unfortunately enrolling infants for this study was difficult, given the prospect of two pH probes and the potential delay in medical therapy. As a result, the number of infants (n=19) was too low for intergroup analysis by ANOVA, yielding a maximum power to detect differences amongst the 4 treatment groups at 65.8% (comparing the pH probe RI values between the OB and PP groups). To adjust for the small numbers, each infant served as their own control, and we compared their

Table 1 Patient Characteristics

ID	Age (Months)	Sex	Smoking in home	Known atopy	First degree relative with atopy/asthma
1	9	Male	Yes	No	Yes
2	13	Male	No	No	Yes
3	5	Male	Yes	No	Yes
5	4	Male	No	No	Yes
7	10	Male	No	No	No
8	6	Male	No	No	Yes
9	10	Male	No	No	Yes
11	14	Female	No	No	No
12	7	Male	No	No	Yes
13	12	Male	Yes	No	No
14*	9	Male	Yes	No	No
15	5	Male	No	No	No
16	4	Female	No	No	Yes
17	13	Female	No	No	Yes
18	9	Male	No	No	Yes
19	9	Male	No	No	Yes
20	6	Male	No	No	Yes
21	4	Male	No	Yes	Yes
22*	11	Female	No	No	No
23	13	Male	No	Yes	Yes
24	12	Male	No	No	Yes
25*	9	Male	No	No	Yes

*did not complete the study.

pre, post and open label time periods using Wilcoxin Signed Rank analysis (Statview 5.0 software, SAS Institute, Cary, NC). A p-value <0.05 was considered significant. This gave acceptable power for comparing pre and post respiratory scores within the OB group (95.7% power) and pre and post daytime cough within the OB group (87.3% power). All other comparisons between the pre and post treatment values achieve less than 70.7% power to detect a statistically significant difference between the observed means. This statistical issues related to the study were reviewed and approved by an independent statistical group at the University of Alberta. All data are expressed as median and interquartile ranges.

Results

Patient characteristics

Twenty-two of 25 infants were enrolled in the study (*Table 1*). Most infants had been given a diagnosis of asthma previously and

were having respiratory problems despite some form of asthma therapy. Three infants were unable to complete the study (2 male, 1 female), two for poor compliance, and one for intercurrent illness. There was a preponderance of boys (18 males, 4 females). There was no significant difference regarding sex in the allocation to treatment groups (one female per group). Median age was 9.0 months (interquartile range of 5.3-12.0 months), again with no difference in allocation to the treatment groups Placebo/Placebo (PP) 8.0 (6.5-9.5, n=4); omeprazole/bethanacol (OB) 7.0 (4.0-12.0, n=6); omeprazole/placebo (OP) 10.5 (7.5-12.5, n=4); bethanacol/placebo (BP) 9.0 (4.8-13.2, n=5). No parent reported any adverse side effect from any of the therapies or diagnostic tests including diarrhea.

pH probe results

In addition to the symptoms of GER, infants were entered into the study if they had evidence of abnormalities on either a pH probe or gastric emptying scan. 15 of the 19

Table 2 pH probe results

	Placebo+Placebo (n=4)		Omeprazole+Bethanacol (n=6)		Omeprazole+Placebo (n=3)		Bethanacol+Placebo (n=5/3)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
pH Probe Score	39.5 (33.0-62.4)	92.6 (67.0-114.6)	60.0 (21.2-141.4)	17.8 (16.1-24.9)	46.7 (25.6-154.6)	13.2 (10.4-14.7)	79.1 (29.4-136.7)	34.6 (20.7-45.3)
Number of Episodes (pH<4)	87.5 (61.5-167.5)	173.0 (112.0-285.5)	141.5 (126-359)	78.0* (41-121)	98.0 (76.3-167.8)	40.0 (34.8-44.5)	102.0 (11.5-421.5)	79.0 (72.3-105.3)
% Time pH<4	8.1 (5.3-11.7)	18.1 (12.2-23.4)	11.3 (3.8-24.9)	2.8* (1.1-3.3)	3.6 (3.0-24.8)	1.3 (0.6-1.7)	11.2 (3.5-21.8)	3.4 (2.4-7)

*P=0.028 after Wilcoxin signed rank analysis of pre vs. post values.

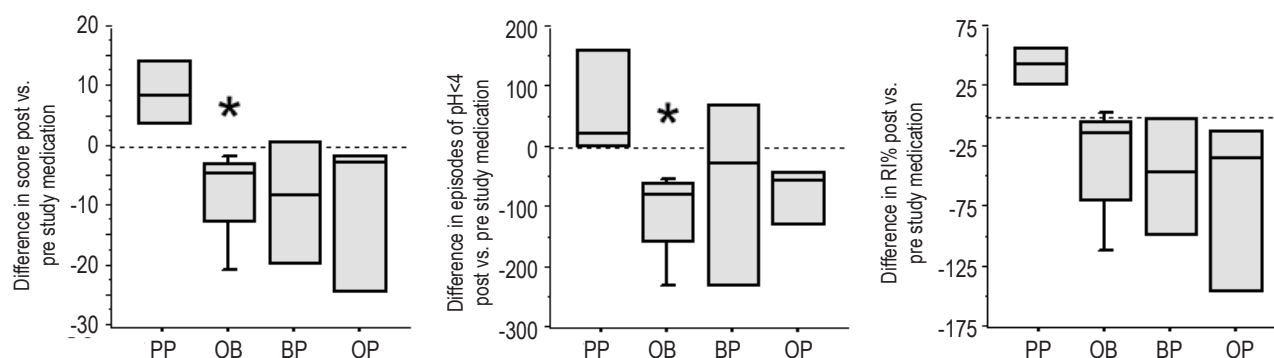


Figure 2 Infants had pH probes done before and after study medications. Compared to pre-study pH probe data, the PP group (white bars, n=4) did not show any improvement in measures of percent time with pH<4 (RI%) (A), the number of episodes with pH<4 (B), or a combined score (C). In contrast, the OB group (n=6) showed a decrease in RI% (p=0.028), a decrease in episodes (P=0.028), and a decrease in score (P=0.07). The OP (n=3) and BP (n=3) groups also showed a decrease in RI%, episodes, and score, but with the smaller number of patients these improvements did not reach statistical significance.

infants displayed increased amounts GER based on percent time with pH<4 (RI%), the number of episodes with pH<4, and a DeMeester score (Table 2). The remaining 4 infants had evidence of GER based on an abnormal gastric emptying scan with parent-observed GER. The degree of GER measured by the pH probe was not statistically different between groups at study entry. After the study period, the PP group was not improved, but tended to get worse untreated over the month as the RI, the number of episodes, and the score all increased (Figure 2). In contrast, the OB group showed a significant improvement in RI and episodes (P=0.028 each) and a trend for improvement in score after a month of therapy. The OP and BP groups also showed some improvement in all categories compared to their study entry values, but with the smaller number of patients, this did not reach statistical significance. All infants

had at least one gastric emptying scan. Thirteen of the nineteen were abnormal at study entry.

Improvement of GI symptoms

All groups displayed frequent episodes of GER symptoms (emesis and/or rumination) at study entry (Table 3). We included rumination in our symptom score as rumination can be very important from a respiratory perspective. Any stomach content coming up to the hypopharynx is potentially harmful to the larynx and lower airway. After one month of therapy, PP did not decrease the amount of GER symptoms compared to their pre-study value (Figure 3A). In contrast, treatment with either OB or OP decreased the number of GER symptoms per day, though given the smaller sample size, this decrease was only statistically significant for

Table 3 Clinical Results

	Placebo+Placebo (n=4)			Omeprazole+Bethanacol (n=6)			Omeprazole+Placebo (n=4)			Bethanacol+Placebo (n=5)		
	Pre	Post	Open	Pre	Post	Open	Pre	Post	Open	Pre	Post	Open
GER	2.0	3.1	0.2	2.3	0.2*	0.2	4.9	1.7	0.5	1.0	2.0	1.4
Episodes/Day	(1.6-3.0)	(2.3-3.4)	(0.1-0.7)	(0.6-6.7)	(0-2.6)	(0-1.0)	(4.2-5.0)	(0-3.9)	(0.2-0.9)	(0.8-10)	(1.0-10.3)	(0.2-8.5)
Coughing	2.9	3.4	1.0	3.4	0.4*	1.0	5.6	2.4	0.9	5.0	3.0	4.3
Episodes/Day	(2.0-5.1)	(2.5-4.9)	(0.5-2.0)	(1.0-6.0)	(0-3.1)	(0.3-1.9)	(3.6-8.3)	(0.5-6.6)	(2.9-6.7)	(4.5-8.9)	(1.0-7.8)	(1.0-6.6)
Respiratory	2.5	3.0	0	3.0	1.5*	0	4.0	1.5	1.5	2.0	1.0	1.0
Score (0-12)	(2.0-4.0)	(2.0-3.5)	(0-1.0)	(2.0-3.0)	(0-2.0)	(0-1.0)	(3.0-5.0)	(0.5-3.0)	(0-4.0)	(2.0-5.3)	(1.0-2.5)	(0-2.3)
Wheezing	1.6	1.9	0.5	2.3	0.9	0.6	0.9	0.2	0.4	1.4	0	0
Episodes/Day	(0.7-3.4)	(0.1-4.6)	(0-2.4)	(0-7.5)	(0.1-2.9)	(0.1-1.6)	(0.3-2.7)	(0.7-0.4)	(0.1-2.0)	(0.3-3.3)	(0-2.5)	(0-1.7)
Coughing	0.6	0.4	0.2	1.1	1.1	0.3	1.3	0.9	0.1	1.5	0.1	0
Episodes/Night	(0.5-0.9)	(0.4-0.6)	(0.1-0.4)	(0.4-2.4)	(0.1-2.0)	(0-1.0)	(1.1-3.9)	(0-2.4)	(0-0.4)	(0.5-2.9)	(0-1.8)	(0-0.6)

*P=0.028 after Wilcoxin signed rank analysis of pre vs. post values.

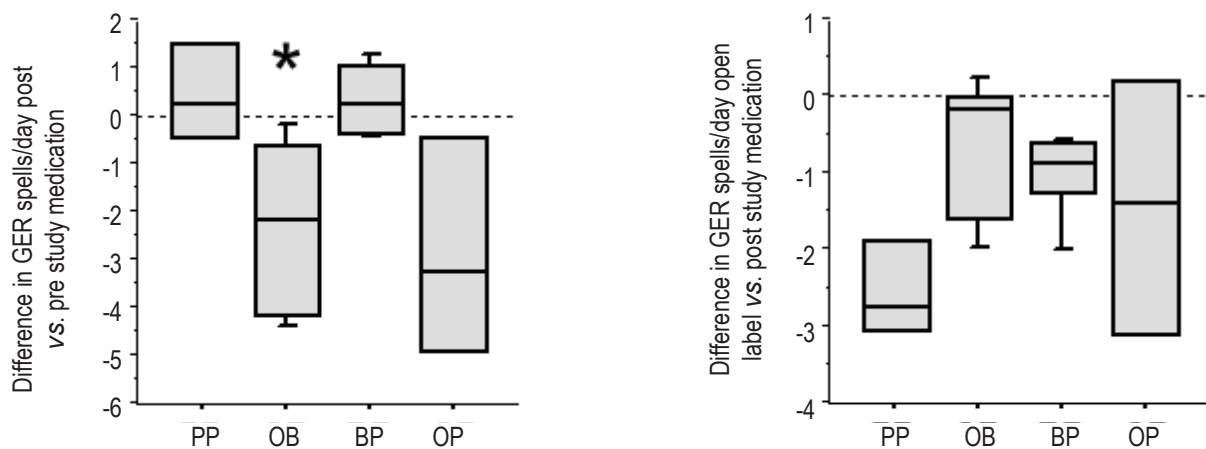


Figure 3 Each infant was assessed for the number of GER events/day (visible emesis and/or rumination). After one-month post-study medication, use of PP did not decrease the amount of GER episodes compared to their pre-study value. Treatment with either OB or OP decreased the number of GER episodes per day compared to their study entry, though this was statistically significant only for the OB group ($P=0.028$). After an open label period of bethanacol and omeprazole, the PP group demonstrated a decrease in GER episodes similar to OB though it did not reach statistical significance ($P=0.06$) (B).

the OB group ($P=0.028$). The BP treatment showed no improvement compared to values their values at study entry. After receiving the open label therapy of bethanacol and omeprazole, the PP group demonstrated a decrease in GER symptoms similar to OB though given the small number of patients, it did not reach statistical significance (Figure 3B, $P=0.06$). Each study drug group also had an open period with some further improvement, but again due to small numbers statistical significance was not achieved.

Improvement of daytime cough

All groups displayed excessive episodes of daytime coughing at study entry, which was not statistically different between groups (Table 3). After one month of therapy, PP did not decrease the amount of coughing compared to the group's pre-study value (Figure 4A). In contrast, the three treatments of OB, OP and BP decreased the number of coughing episodes per day, which was statistically significant for the OB group ($P=0.028$). After receiving the open label therapy

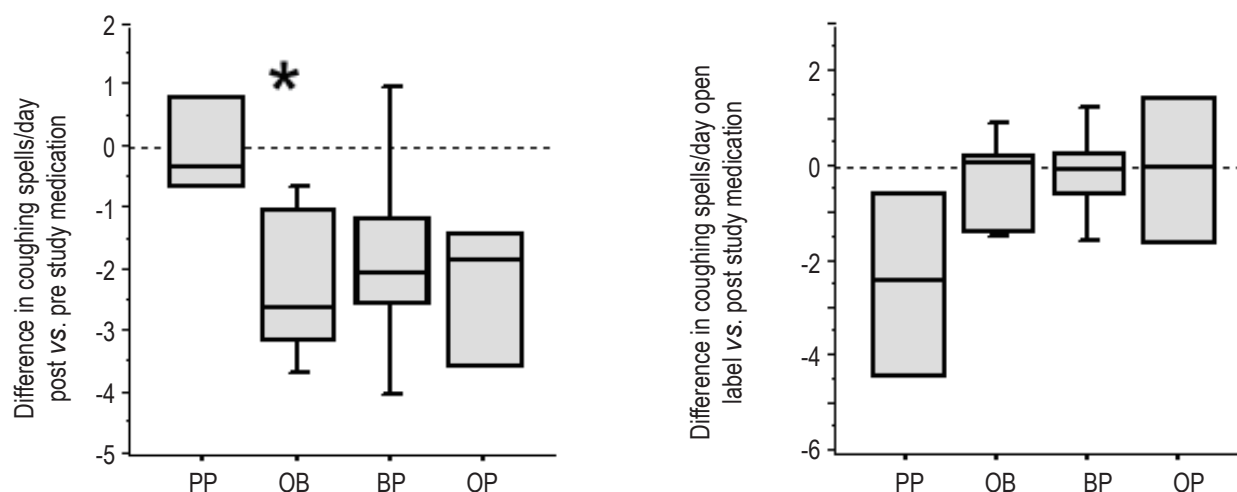


Figure 4 Each infant was assessed for coughing spells/day. Post-therapy, PP (n=4) did not decrease the amount of coughing compared to the group's pre-study value (A). In contrast, the three treatments of OB (n=6), OP (n=4), and BP (n=5) did decrease the number of coughing episodes per day, but these data only reached statistical significance for the OB group ($P=0.028$). After open label therapy of bethanacol and omeprazole, the PP group demonstrated a decrease in cough that was similar in magnitude to the OB study period though it did not reach statistical significance ($P=0.06$, *Figure 3B*).

of bethanacol and omeprazole, the PP group demonstrated a decrease in cough that was similar in magnitude to the OB study period though it did not reach statistical significance ($P=0.06$, *Figure 4B*). Each study drug group also had an open period with further minor improvement in cough.

Improvement of respiratory scores (RS)

At study entry, all infants had evidence of abnormal respiratory scores, which were similar among the groups (*Table 3*). After the study period, infants on PP showed only a minor change in RS. In contrast, infants on study drugs showed improvement in their RS, which reached statistical significance for the OB group ($P=0.04$). After being on open label double therapy, PP also showed a similar degree of improvement compared to OB, though due to small sample size, it did not reach statistical significance ($P=0.10$). Each study drug group also had an open period with some further improvement (*Figure 5*).

Improvement of wheezing and nighttime cough

All groups displayed similar degrees of wheezing and nighttime cough episodes at study entry (*Table 3*). After one month of therapy, PP did not decrease wheeze or nighttime cough compared to study entry data. The three treatment

groups of OB, OP and BP appeared to have less complaints of wheezing or nighttime cough episodes per day, though statistical significance was not reached for any category. Combining all infants into one group and comparing the pre study values of cough and wheeze to the open label values, treatment of GER did cause a statistically significant decline in the amount of wheezing and nighttime cough ($P=0.027$ and $P=0.002$ respectively).

Parents and physicians agreement regarding study medications

At the end of each study period, both parents and physicians were asked if they thought their infant was improving on therapy. While blinded on the study medication, neither parents nor physicians saw a significant improvement for infants on PP (n=4). In contrast, despite being blinded, physicians and parents were unanimous in their impression that infants on OB were better compared to their condition at study entry (n=6). Of four infants on OP, three were unanimously improved, and one was considered better by the parent but the same by the physician (n=4). There was no clear consensus about infants on BP and one physician felt one infant was worse (n=5). After being on open label, parents and physicians of PP infants unanimously agreed that there was an improvement. Infants from the other

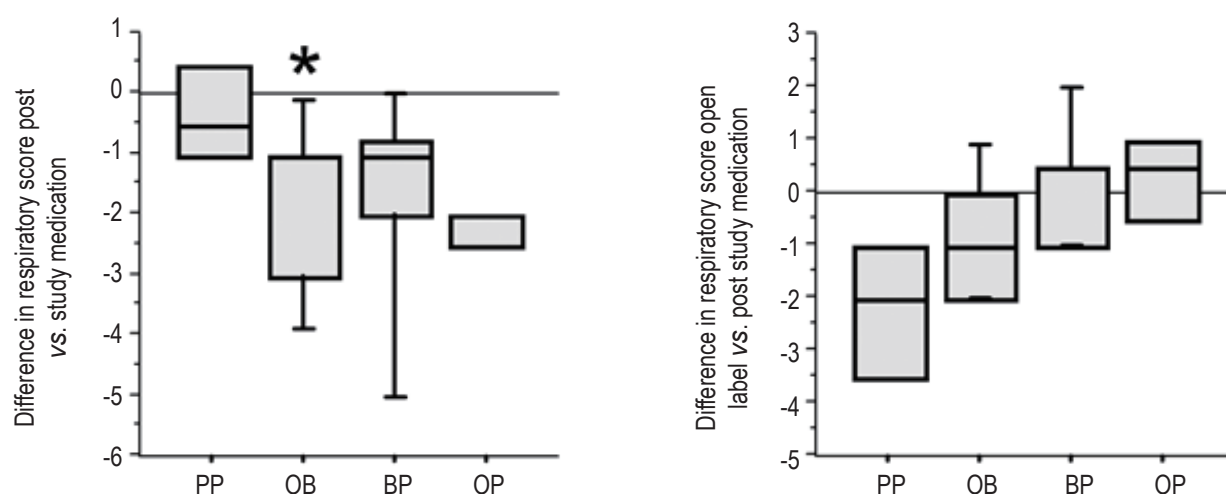


Figure 5 Treatment of GER improved respiratory scores (RS). At study entry, all infants had evidence of abnormal respiratory scores, which were similar among the groups (A). After the study period, PP did not improve the RS (n=4). The three treatments of OB (n=6), OP (n=4), and BP (n=5) did decrease the RS, but these data only reached statistical significance for the OB group (P=0.04). After being on open label double therapy, PP also showed an improved RS though it did not reach statistical significance (P=0.10) (B).

three groups (n=15) also showed further improvement on open label, and 6 felt their infant was much better compared to study entry.

Discussion

The perception that GER can induce lung diseases in older children and adults has been well characterized (5,19-22). While the association of GER and aspiration in infants was described at least as early as 1978 (23), few studies have specifically addressed management from a pediatric lung perspective. In a study by Sheik *et al.*, 64% of infants with persistent wheezing had excessive GER, as measured by a standard pH probe (9). Of the infants with proven GERD via pH probe, 64% improved on cisapride with ranitidine and were able to avoid inhaled corticosteroids.

The proton pump inhibitor omeprazole is superior to ranitidine in its ability to block acid secretion (6,24). The dissolvable tablet formulation also makes it reasonable for compliance in infants. Thus, the choice of omeprazole for this study was relatively clear. Since the inception of this study newer proton pump inhibitors have also come on the market for this age group (25). The choice of a motility drug in the treatment of GER was less clear. Cisapride is no longer available. It has been common practice to use prokinetic drugs, such as metaclopramide, or domperidone to “decrease GE reflux” despite no controlled studies to

prove that these drugs do decrease reflux in infants, and ample studies to show that they do not (26-28). Bethanacol (Urecholine®) is a parasympathomimetic-agent, which stimulates gastric motility, increases gastric tone and affects motility (11,29). We have experienced a positive impression of its effectiveness in infants, thus we were interested to see its performance in a controlled setting. Neither bethanacol nor omeprazole had been studied in infants with GER related respiratory disease prior to this study.

In this study, we demonstrate that within a relatively brief period of time, all of our infants with increased GER showed significant improvement in their respiratory status if adequately treated for acid exposure. While it is not possible to make strong statements, given our low sample size, the best prevention of GER episodes, as measured by GI symptoms and pH probe, appears to be the combination of an acid suppressor (omeprazole) and a motility-altering agent (bethanacol). In association, both parents and physicians who were blinded to the study medications during the first month consistently agreed that there was a clinical improvement in the infants’ respiratory status on this combination therapy. In contrast, both parents and physicians observing infants treated with placebo alone saw no improvement in respiratory parameters, clinical impression, or GER events. Switching from placebo to combination therapy led to a trend in improvement of GI and respiratory outcomes, but because of the small

number of patients in this subgroup, statistical significance was not reached. This is the first randomized controlled study of a proton pump inhibitor and a prokinetic agent in young children determining both the effects on GER and respiratory symptoms.

Managing infants with chronic cough and wheeze is difficult compared to that in older children. At this age, pulmonary function testing, including measurement of airway hyperresponsiveness, is more difficult and is not established in most clinical settings. The diagnosis largely relies on the symptoms of chronic cough and/or wheeze. While there are selected populations of infants at higher risk of asthma that do respond well to inhaled corticosteroids (30), most infants in the general population with chronic cough and/or wheeze do not (31). It is becoming evident that in some neurologically normal infants who have frequent chest problems the cause is not asthma, but pulmonary aspiration. Chronic pulmonary aspiration can lead to airway obstruction in the form of bronchitis and bronchiectasis (32,33).

The clinical dilemma has been in identifying this population. In the Sheikh study, 44% of infants had no visible emesis as recorded by the parents, and the diagnosis of possible GER associated pulmonary disease would not have been considered if not for the pH probe (9). This was called “silent” reflux. Thus, physician awareness of this possible diagnosis was needed as only directed diagnostic tests could clarify the etiology of the breathing difficulty. Another issue is that standards for the tests of abnormal GER are based on esophageal and not respiratory pathology (34). Standards for “normal” reflux are based on pH probe measurements in the distal esophagus usually 5 cm above the lower esophageal sphincter. The diagnosis of GERD with a standard single sensor pH probe in the lower esophagus does not consider that refluxate to the airway could be pathologic. Clearly, the squamous cell esophageal lining is better designed to handle food and acid than the columnar epithelium of the airway. In the most recent international meeting of gastroenterologists they published a consensus statement suggesting “a patient-orientated approach that is independent of endoscopic findings” when considering extra-esophageal pathology (5). Because a double sensor pH probe measures both distal and proximal esophageal pH, the double sensor pH probe has been suggested to be superior compared to the single lumen system when studying issues related to airway disease (35,36). Further, we have observed that the upper esophageal sensor may not correlate with risk of aspiration if it is placed below the upper esophageal

sphincter (UES). Thus, we have been routinely placing the upper sensor in the hypopharynx. Because the current literature is so limited for standards of double sensor data, the ability to use it as a diagnostic tool has been limited (34). Work using esophageal impedance measurements would suggest that non-acidic refluxate is also important in pulmonary disease (37,38). Ideally, combined pH and impedance measurements would have been the better choice of diagnostic. Unfortunately, esophageal impedance measurements were not available at our center when this study began.

The other confounding factor in diagnosing GER-related lung disease is the quality of the swallowing mechanism. The intact airway closure mechanism of the larynx usually allows humans to eat and drink without compromising the lung (39), thus refluxed pharyngeal fluid does not necessarily equate with pulmonary aspiration. In cases of some children with apparently no neurological impairment, there can be an inability to consistently protect the airway when fluid is in the hypopharynx (33,40). Individuals with swallowing dysfunction are at higher risk of pulmonary aspiration. Ideally, we had hoped to have all our infants evaluated by speech pathology and radiology. Unfortunately, we were unable to obtain modified barium swallows to be performed in a timely manner before study entry. Thus, these data cannot be shown. We did ask parents questions about the signs of swallowing dysfunction before enrolling children, and we attempted to not enroll infants in whom the signs of direct aspiration were more obvious than the signs of indirect aspiration from GE reflux. That being said, we believe that often direct aspiration from swallowing dysfunction often improves after treatment of excessive GER.

From the Tucson Children's Respiratory Study, it has been accepted that most infants with wheeze outgrow their chest difficulties by childhood and adolescence (41). The Tucson group of infants with wheeze was divided between those with risk factors for asthma and those without. Those with no wheeze during infancy had the best lung function at 16 years old. Those with wheeze but without risk factors were called the ‘transient wheezers’ because they did not appear to have asthma in later childhood and adolescence. Despite their absence of wheeze in adolescence, the ‘transient wheezers’ continued to have significantly poorer lung function compared to those adolescents that never wheezed in infancy. The design of most infant cohorts suggests that GERD-related disease is excluded from the study. Unfortunately, pH probe or gastric emptying scans

are not part of the selection criteria, nor are questions about pulmonary aspiration. Given the consistent problem of silent GER, it is likely that a significant number of these infant wheezers could have GER-related disease (42).

The transient nature of the wheeze is also suggestive of pulmonary aspiration as an underlying diagnosis. Most neurologically normal infants seem to get better over time, though there are no long-term follow-up studies to back this assertion. The reason for improvement could be from more time in an upright position, decreased feeding of a liquid diet, maturation of the swallow, or decreased respiratory rate. In the Tucson study, the deficit in lung function in 'transient wheezers' never recovered to that of normal or later onset wheezing infants (41). There is data that infants with GERD have persistence of esophageal disease for longer than is clinically apparent, and that these infants go on to have adult GERD (3,43). Thus, while the Tucson data is reassuring that most transient wheezers improve by age 6-16, a longitudinal study of infants with pulmonary aspiration followed for the effects on adult lung function is needed.

In the Sheikh study, the infants with a higher risk of asthma were less likely to have increased GERD and tended to require anti-asthma therapy despite treatment for GERD (9). In our study, infants were not selected for their atopic status or family history of asthma, and many were already failing inhaled corticosteroid therapy. Thus, we could have been biased toward a more non-atopic phenotype of infant wheezer.

Enrolling infants for this study was difficult, given the prospect of two pH probes and the potential delay in medical therapy. Despite the small number of patients in this study, we found the data compelling because of the clear and relatively rapid improvements in the respiratory status. The children in this study were referred for significant respiratory symptoms despite reasonable outpatient therapy. The parents were quite motivated to subject their children to two pH probes to determine whether GER was playing a role. Thus, while we agree with a recent publication by Khoshoo *et al.* that more focus should be placed on non-medical therapies for GER symptoms (44), we believe our patients did warrant therapy. There are many opinions on the management of cough and wheeze in infancy, but few good studies of anti-GER therapy at this age. Based on this randomized placebo-controlled trial, we suggest that infants with chronic symptoms of excessive GER, cough and wheeze, especially those who have failed inhaled corticosteroids, should be considered for anti-GER therapy.

The combination of bethanacol and omeprazole appears to be effective.

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Footnote

Conflicts of Interest: DJ Adamko was an AHFMR Clinical Investigator. The other authors have no conflicts of interest to declare.

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