ORIGINAL ARTICLE

Effect of Gaviscon Infant on gastro-oesophageal reflux in infants assessed by combined intraluminal impedance/pH

R Del Buono, T G Wenzl, G Ball, S Keady, M Thomson

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See end of article for authors' affiliations
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Correspondence to:
Dr M Thomson, Centre for Paediatric Gastroenterology, Sheffield Children's Hospital, Western Bank, Sheffield S10 2TH, UK; mike.thomson@sch.nhs.uk

Accepted
12 November 2004
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Background: Gaviscon Infant (GI) has been recommended for gastro-oesophageal reflux (GOR) in infants. Its efficacy has not been examined with a physiologically appropriate denominator to define the degree of GOR.

Aim: To investigate the influence of Gaviscon Infant on GOR in infants using combined pH and intraluminal impedance measurement.

Methods: Twenty infants (mean age 163.5 days, range 34–319 days) exclusively bottle fed, with symptoms clinically suggestive of GOR, underwent 24 hour studies of intra-oesophageal 6 channel impedance and dual channel pH monitoring, during which six random administrations (3+3) of Gaviscon Infant (625 mg in 225 ml milk) or placebo (mannitol and Solvito N, 625 mg in 225 ml milk) were given in a double blind fashion. Impedance/pH reflux data were recorded and analysed blind by one observer.

Results: The median number of reflux events/hour (1.58 v 1.68), acid reflux events/hour (0.26 v 0.43), minimum distal or proximal pH, total acid clearance time per hour (time with pH below pH 4), and total reflux duration per hour were not significantly different after GI than after placebo. Reflux height was marginally lower after GI (median 66.6% v 77.3% oesophageal length) compared with placebo.

Conclusions: Results showed a marginal but significant difference between Gaviscon Infant and placebo in average reflux height, and raises questions regarding any perceived clinical benefit of its use.

Gastro-oesophageal reflux (GOR) is the regurgitation of gastric contents into the oesophagus and is a physiological occurrence in all individuals. It is particularly frequent in infants and is probably largely physiological, usually resolving spontaneously.[1] GOR may become pathological when it causes symptoms such as heartburn, oesophagitis, acute life threatening events, and respiratory disease.[1–3] Known consequences of GOR in infants are irritability, faltering growth, anaemia, and respiratory events such as aspiration pneumonia.[1 2] Studies by Carre[4] suggested that only 5–10% of children with vomiting or regurgitation in infancy continued to have symptoms after the age of 4 years. More recent studies showed that 19% of infants with pathological GOR still have symptoms at 18 months of age.[5] Currently available techniques for the study of non-acid (pH >4, <7) or alkaline reflux include ultrasound, bronchoalveolar lavage, scintigraphy, fluoroscopy, bilirubin monitoring, and pH monitoring.[6–10] These methods fall far short of the ideal as they only measure a short time window and do not allow for symptom/event temporal correlation.

Oesophageal pH monitoring has gained general acceptance as the method for assessment of GOR in children, and is regarded as the investigation of first choice in infant GOR disease, especially if respiratory in manifestation.[1 3 8 9 11] However, pH measurements cannot detect GOR in the pH range 4.0–7.0 due to the proximity to the normal oesophageal pH. Consequently, pH metry misses many episodes of postprandial reflux in infants because of neutralisation of gastric contents by milk formula for 1–2 hours after a meal as it simply measures the H^+ ion concentration at the sensor site. Therefore the terms "acid", "neutral", or "alkaline" "GOR" should be preferred to the blanket term "GOR". Because the occurrence of GOR associated symptoms may be independent of pH, a pH independent technique that facilitates ambulant 8–24 hour measurement for GOR detection has been established and relies on differing conductivities of luminal contents. This is termed multiple intra-luminal impedance (IMP)/pH and has been described in detail previously.[12–14] This allows for the first time the physiologically appropriate assessment of treatment efficacy for GOR.

New insights into the effect of Gaviscon Infant on acid and non-acid GOR/GORD in infants will be of value in the differential indication and guidance of therapy.

The main aim of this randomised, placebo controlled, double blind study was the investigation of the influence of Gaviscon Infant on GOR in infants using this new technique.

PATIENTS AND METHODS

The study included 20 patients (11 male, 9 female) of median age 163.5 days (range 34–319). Patients were eligible if they were under 12 months of age, had symptoms clinically suggestive of GOR (for example, regurgitation >3×/day any amount *or* >once/day half the feed), were over 2000 g in weight, were exclusively bottle fed formula milk or expressed breast milk, and had no signs of acute infection. Patients who were taking acid suppressing or motility agents had therapy stopped at least three days (five days in the case of omeprazole) before beginning the study.

The study protocol was approved by the Royal Free NHS Trust Ethical Review Committee, with informed parental/guardian consent obtained. On the day of simultaneous IMP/pH measurement, patients were fasted for a period of at least three hours. An IMP catheter (diameter 2 mm) with two pH sensitive antimony electrodes and seven impedance electrodes (Sandhill Scientific, Inc.) was used (see fig 1). Changes in intra-oesophageal impedance were measured along this catheter as described in previous work.[12–14] The catheter was placed. transnasally, and positioned using the Strobel formula,[1] with total measuring segments reaching from approximately 1.5 cm above the lower oesophageal sphincter

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Abbreviations: GI, Gaviscon Infant; GOR, gastro-oesophageal reflux; IMP, impedance; LOS, lower oesophageal sphincter
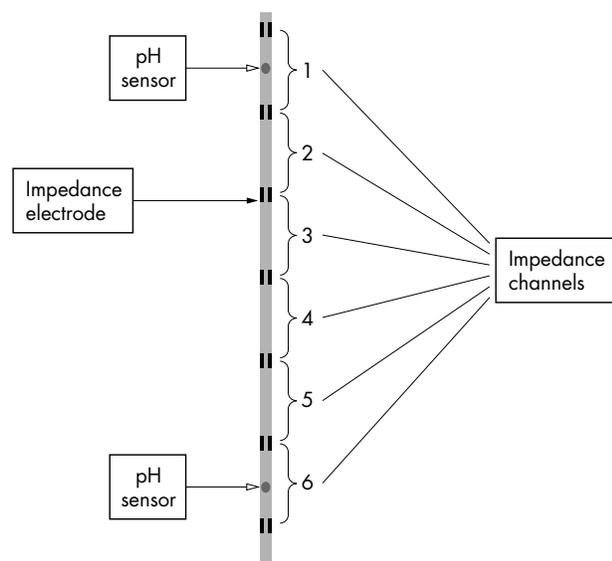
Figure 1 Schematic representation of the impedance catheter with seven impedance electrodes set at 1.5 cm intervals and comprising six measuring segments (impedance channels). Distal and proximal pH electrodes were also incorporated to detect the pH of the refluxate at approximately 2 cm above the lower oesophageal sphincter (LOS) and in the upper oesophagus.

(channel 6) to the upper oesophagus (channel 1), both of which also had pH sensors. The beginning and end of feeding periods were entered on screen in real time, and recordings were made for 24 hours. During this 24 hour period, six random administrations (3+3) of Gaviscon Infant (Reckitt Benckiser Healthcare (UK) Ltd) (625 mg in 225 ml milk) or placebo (mannitol and Solvito N to ensure similar appearance and taste, 625 mg in 225 ml milk) were given in a double blind fashion and with one observer. Gaviscon Infant consists of sodium and magnesium alginate and mannitol; it does not contain bicarbonate. The placebo does not pharmacologically alter the pH of gastric contents. All impedance recordings were visually analysed, blind to type of feed used, for the typical IMP pattern of GOR indicated by a retrograde oesophageal volume flow (see fig 2). All GOR episodes were subdivided by their pH values. In addition, the distribution of GOR episodes was determined for each measuring period, defined by postprandial time. The height reached by the refluxate in the oesophagus, and volume and acidity clearance were registered for each GOR episode. Data sets for each patient before and during treatment with Gaviscon Infant or placebo were compared.

The following parameters were derived from the pH and impedance traces:

(a) Study duration
(b) Number of reflux events (and number of reflux events per hour)
(c) Number of non-acid reflux events (and number of non-acid reflux events per hour)
(d) Number of acid (pH <4) reflux events (and number of acid reflux events per hour)
(e) Number of reflux events in the first two hours after the feed
(f) Average reflux height (based on the "height" (the highest impedance electrode) at which each reflux event was detectable)
(g) Average minimum distal pH
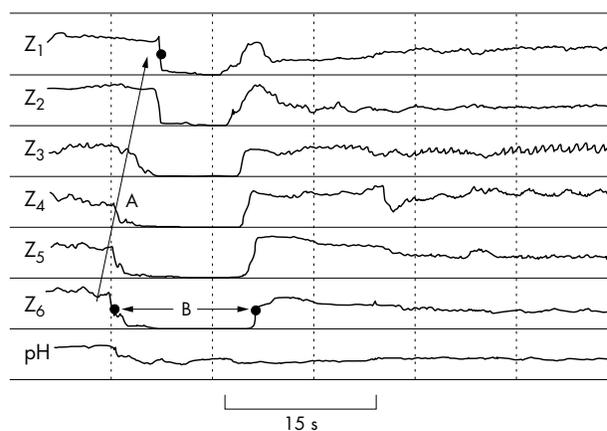(h) Average minimum proximal pH

Figure 2 Impedance pattern typically observed during a reflux episode. In this example only the distal pH channel is shown which is located approximately 1.5 cm above the LOS. The retrograde oesophageal flow is indicated by arrow A. In this example the reflux reaches the proximal (highest, Z_1) channel. The reflux duration is indicated by arrow B. The pH of the reflux can be derived from the pH channel and the acid clearance is the time taken for the pH channel wave to reach pH 4.

(i) Total acid clearance time per hour (total time with distal pH below pH 4 relative to study duration) for acid reflux events
(j) Total reflux duration time per hour (based on the impedance traces).

Parameters (b), (d), (e), (f), (g), (h), (i), and (j) were summarised for each treatment and the differences between treatments were assessed using the Wilcoxon signed rank test. The number of reflux events per hour was compared between the period consisting of the first two hours after feeding for each feed and the residual period until the next feed. Data for each treatment were assessed independently.

RESULTS

Table 1 summarises the main results by treatment between Gaviscon Infant and placebo. A total of 747 reflux events were detected by IMP of which 518 were non-acid and 229 were acidic (pH <4). The median number of reflux events per hour, median number of acid reflux events per hour, and median number of reflux events during hours 1 or 2 were all slightly lower after Gaviscon Infant than after placebo, but were not statistically significantly different. Average reflux height was marginally lower after Gaviscon Infant (median 1.90 equating to reaching proximally 66% of oesophageal height from GOJ) compared with placebo (median 1.31, equating to reaching 77.3% of oesophageal height from gastro-oesophageal junction), and was the only parameter statistically significantly different from zero (p < 0.001). There were no statistically significant differences between Gaviscon Infant and placebo in average minimum distal or proximal pH.

DISCUSSION

We have described a placebo controlled, randomised, double blind study to investigate the influence of Gaviscon Infant on GOR in infants by using the novel and physiologically appropriate technique of combined pH and intraluminal impedance measurement. The only parameter to achieve statistical significance for a positive effect after Gaviscon Infant compared with placebo was a marginally lower average height reached up the oesophagus by the refluxate. There were no statistically significant differences between Gaviscon Infant and placebo in average minimum distal or

Table 1 Summary of placebo versus Gaviscon Infant differences

Parameter	Difference (Placebo − Gaviscon Infant)	p value*
Number of reflux events per hour		
Range	−1.20 – 3.80	
Median	0.06	0.784
Number of acid reflux events per hour		
Range	−0.55 – 3.94	
Median	−0.02	0.940
Number of reflux events in hours 1 or 2		
Range	−11 – 19	
Median	1.0	0.155
Average reflux height		
Range	−1.40 – 0.17	
Median	−0.56	<0.001
Average minimum distal pH		
Range	−1.00 – 1.23	
Median	−0.30	0.411
Average minimum proximal pH		
Range	−0.98 – 1.15	
Median	−0.31	0.225
Total acid clearance time per hour (s/h)		
Range	−19.5 – 239.8	
Median	0.9	0.322
Total reflux duration per hour (s/h)		
Range	−38.5 – 111.8	
Median	7.6	0.096

*p values from Wilcoxon signed rank test.

proximal pH. The median number of reflux events per hour and median number of acid reflux events per hour, the median total acid clearance time per hour (time with pH below pH 4), and the median total reflux duration per hour were all lower after Gaviscon Infant than after placebo, but did not reach statistical significance.

The technique of combined pH and impedance procedure allows detection of both acid and non-acid reflux episodes—the latter therefore undetectable by conventional pH metry. Wenzl and colleagues[13] found that 78% of reflux episodes causing apnoea in infants were non-acid, and showed that of 1887 IMP determined reflux episodes recorded in 50 patients, only 282 (14.9%) were acidic.[14] In this study the vast majority of 747 reflux events detected by impedance would not have

Figure 3 After treatment with Gaviscon Infant, while the number of reflux events per hour was lower from 2 hours after feeding, compared with the first two hours after feeding, the difference in the number of reflux episodes per hour was not statistically significant. After treatment with placebo, the number of reflux events per hour was markedly lower from 2 hours after feeding, compared with the first two hours after feeding, and the difference was statistically significant (p < 0.001). pph, postprandial hour.

been detected by the so-called "gold standard"—that is, pH metry.

Our results show that most GOR episodes occur during the first two postprandial hours. The median number of reflux events during the first two postprandial hours were all lower after Gaviscon Infant than after placebo compared to the time following two hours after feeds (p < 0.001). The clinical finding that the majority of GOR events occur during the first two postprandial hours supports the necessity to detect the neutral or weak acid GOR (undetectable by standard pH studies) during this time span, and not possible for a physiologically appropriate time frame by other methods such as sonography, barium radiography, scintigraphy, external electrical impedance tomography, and manometry which generally only afford a short time window. In this regard IMP technique is ideal for GOR detection in infants having frequent milk feeds.[15]

IMP accurately measures the oesophageal height reached by refluxates, and in this study we have shown that the average reflux height was lower after Gaviscon Infant compared with placebo. The adult preparation Liquid Gaviscon (sodium alginate and potassium bicarbonate) acts as a raft floating on the stomach contents and then coats the oesophagus, acting as a movable neutral sealant that occupies the oesophageal space when a gastric pressure wave pushes it into the oesophagus as a reflux waves enters it from the stomach.[16] Gaviscon Infant, however, does not contain bicarbonate, and therefore it does not form a raft but acts as a thickening agent. Our results are in accordance with those of Wenzl and colleagues,[17] who studied the effects of thickened feeding on GOR in infants and reported a reduction in reflux height in patients after they were fed with thickened milk; similarly no difference was observed in acid reflux events before and after treatment.

The majority of studies assessing efficacy of Gaviscon use have used the hydroxide containing preparations; these buffered the gastric contents and furthermore were assessed using the incorrect physiological denominator of pH study—results unsurprisingly have been inconclusive.[18–20]

The physiologically appropriate denominator has been used in this study to objectively study in a randomised, placebo controlled way the effect of Gaviscon Infant on infant reflux;
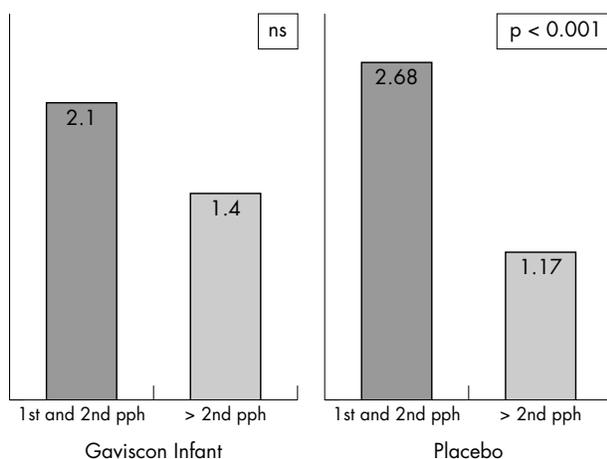
findings do not suggest a significant effect of this preparation on reflux in this population except for a marginal decrease in the height of the refluxate proximal migration up the oesophagus. Any observed clinical effect of this preparation must therefore be assumed to be either of a placebo nature, or due to a different physiological mechanism, such as the potential coating of the lumen of the oesophagus as a protecting layer.

ACKNOWLEDGEMENTS

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Authors' affiliations

R D Buono, G Ball, M Thomson, Centre for Paediatric Gastroenterology, Royal Free and University College Medical School, London, UK
T G Wenzl, Kinderklinik der RWTH Aachen, Aachen, Germany
S Keady, Pharmacy Department, Royal Free and University College Medical School, London, UK

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Jack Maypole