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

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.2–4 Known consequences of GOR in infants are irritability, faltering growth, anaemia, and respiratory events such as aspiration pneumonia.2–6 Studies by Carre4 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.7 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.8–10 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.7,8,9,11 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 post-prandial 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.

Abbreviations: GI, Gaviscon Infant; GOR, gastro-oesophageal reflux; IMP, impedance; LOS, lower oesophageal sphincter
Infant or placebo were compared. For each patient before and during treatment with Gaviscon clearance were registered for each GOR episode. Data sets refluxate in the oesophagus, and volume and acidity defined by postprandial time. The height reached by the GOR episodes was determined for each measuring period, subdivided by their pH values. In addition, the distribution of oesophageal volume flow (see fig 2). All GOR episodes were visually analysed, blind to type of feed used, for the typical IMP pattern of GOR indicated by a retrograde (highest, Z1) 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.

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 proximal pH.
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\textsuperscript{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.\textsuperscript{14} In this study the vast majority of 747 reflux events detected by impedance would not have 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.\textsuperscript{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 reflux waves enter it from the stomach.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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;

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diff (Placebo – Gaviscon Infant)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of reflux events per hour</td>
<td>– 1.20 – 3.80</td>
<td>0.784</td>
</tr>
<tr>
<td>Range</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>– 0.55 – 3.94</td>
<td>0.940</td>
</tr>
<tr>
<td>Number of acid reflux events per hour</td>
<td>– 0.02</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>– 11 – 19</td>
<td>0.155</td>
</tr>
<tr>
<td>Median</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Average reflux height</td>
<td>– 1.40 – 0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Range</td>
<td>– 0.56</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>– 1.00 – 1.23</td>
<td>0.411</td>
</tr>
<tr>
<td>Average minimum distal pH</td>
<td>– 0.98 – 1.15</td>
<td>0.225</td>
</tr>
<tr>
<td>Range</td>
<td>– 0.31</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>– 0.30</td>
<td></td>
</tr>
<tr>
<td>Average minimum proximal pH</td>
<td>– 0.98 – 1.15</td>
<td>0.001</td>
</tr>
<tr>
<td>Range</td>
<td>– 0.31</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>– 0.30</td>
<td></td>
</tr>
<tr>
<td>Total acid clearance time per hour (s/h)</td>
<td>– 19.5 – 239.8</td>
<td>0.322</td>
</tr>
<tr>
<td>Range</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total reflux duration per hour (s/h)</td>
<td>– 38.5 – 111.8</td>
<td>0.096</td>
</tr>
<tr>
<td>Range</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p values from Wilcoxon signed rank test.

**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.
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
We thank John Sykes for statistical analyses, Reckitt Benckiser for funding Dr Del Buono, and Sandhill Scientific, Inc. (Colorado, USA) for the kind donation of the impedance apparatus.

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Competing interests: Reckitt Benckiser Healthcare (UK) Ltd, the producers of Gaviscon Infant, funded one of the authors (Dr R Del Buono)

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Arch Dis Child 2005 90: 460-463
doi: 10.1136/adc.2002.024463

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