Dual pH probe monitoring versus single pH probe monitoring in infants on milk feeds: the impact on diagnosis

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Abstract

***Objectives*—Oesophageal pH monitoring is the gold standard technique for the detection of gastro-oesophageal reflux in adults and children. A standard parameter used to define "abnormal" reflux is the percentage of recording time for which the gastric pH is < 4. This study investigated the relevance of this measure in infants on regular milk feeds whose gastric contents and refluxate will be neutral for most of the recording time.**

***Methods*—Simultaneous oesophageal and gastric pH monitoring was carried out on all infants who were milk fed exclusively and admitted to hospital for suspected gastro-oesophageal reflux. In vitro studies were performed to establish the buffering capacities of the fruit juice, Dioralyte (a glucose electrolyte solution), breast milk, and milk formula feeds available on the paediatric wards.**

***Results*—Complete sets of data were obtained from 30 babies with a mean age of 4 months. Gastric pH was ⩽ 4 for a mean (SEM) of 42.4 (4.9)% of the recording time. The mean (SEM) percentage time that oesophageal pH was < 4 for the total recording period was 6.89 (0.92)%. Recalculation of the percentage of time that the gastric pH was > 4 increased this value to 17.81 (2.46)%. Using a cut off point of 10%, 11 of the 30 babies would have been diagnosed positive for reflux using the conventional method; however, recalculation by ignoring the time for which gastric pH was high doubled this to 22 positive for reflux.**

***Conclusion*—Combined oesophageal and gastric pH monitoring greatly increases the number of positive results from tests in infants on regular milk feeds.**

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The reflux of gastric contents in neonates is recognised to be of considerable clinical importance. Children with "suspected" gastro-oesophageal reflux (GOR) typically account for ~ 20% of all new paediatric outpatient referrals, making it the third most common reason for gastroenterology consultations. Seventy per cent of cases of apnoea can be attributed to GOR,[1] and links with apparent life threatening events have also been reported. However, we have reason to believe that GOR is even more common than is supposed, and is the hidden factor behind many other childhood problems. Thus, it is clear that accurate diagnosis is of crucial importance.

Oesophageal pH monitoring is regarded as the gold standard technique for the detection of GOR in both adults and children.[2] However, diagnosis and study of neonatal reflux is much more difficult than corresponding studies in adults. The standard parameter used for the diagnosis of abnormal reflux is the percentage of time over 24 hours during which oesophageal pH is < 4, or the Demeester score. This measure is intended to provide an indication of risk of occurrence of oesophagitis, but in neonates this risk is largely irrelevant because a single event might be sufficient to cause an apparent life threatening event. Paediatric oesophageal pH traces are often described as "abnormal" or "unusual" when the classic scoring systems return a figure within the normal range. This is particularly problematic because interpretation of the data is increasingly performed by software rather than by skilled inspection. Adults tend to eat three meals a day and between these meals gastric pH is low and can be detected. In newborn babies feeding is frequent, usually three to four hourly throughout both the day and night, with milk, which is a good buffer. This leads to the pH of the gastric contents being raised for prolonged periods. Under these circumstances, pH monitoring will lead to a high rate of false negative diagnoses, because reflux of the neutral gastric contents will be unscored using conventional criteria.

The aim of our study was to assess the extent to which protocols based on adult reflux might be compromised by neonatal feeding regimens. Gastric pH was monitored in addition to oesophageal pH, to identify periods in which gastric pH was > 4. These data were used to perform reanalysis of the oesophageal pH to reject periods for which the refluxate would not be scored by conventional methods. To design a feeding regimen that would increase the sensitivity of the test by lowering the gastric pH, the buffering capacity of the routinely used infant feeds was established in vitro.

Methods

IN VITRO STUDIES

The aim of this part of the study was to assess the buffering capacities of the milk feeds and supplementary clear liquids used routinely on the paediatric wards of the Queen's Medical Centre, Nottingham.

Materials
Seven commercial infant milk formulas (Cow and Gate Premium (Cow and Gate, Trowbridge, UK), Pepti-Junior (Cow and Gate), Pregestimil (Bristol-Myers, Hounslow, UK), SMA Gold (SMA Nutritions), Prosobee (Bristol-Myers), Neocate (Scientific Hospital Supplies International, Liverpool, UK), and Farley's Milk (Farleys, Plymouth, UK), breast milk, and two clear liquids (Robinsons "Apple and Cherry" fruit juice, and Dioralyte (Rhone-Poulenc Rorer, Eastbourne, UK), an electrolyte supplement) were tested. These samples were obtained from the kitchens of the paediatric wards, with the exception of breast milk, which was donated by mothers from the neonatal care unit, Queen's Medical Centre. The composition of the feeds is detailed in table 1.

Equipment
A pH sensitive glass probe (Radiometer A/S, Copenhagen, Denmark) connected to a solid state recorder (Memolog; Novo Diagnostic Systems, Copenhagen, Denmark) was used to measure pH. The pH probes were calibrated and maintained routinely according to the manufacturer's instructions.

Protocol
An aliquot of 10 ml of each test sample was prepared at its standard feed concentration. Breast milk was used immediately after it was expressed.

The test samples were placed in a beaker situated in a water bath at 37°C. After the temperature of the sample had stabilised, a five minute baseline recording of pH was made. Hydrochloric acid (0.03 M), warmed to 37°C, was pumped into the beaker at a rate of 4 ml/minute and the mixture was well stirred. The pH recording was monitored continually to ensure that accurate recordings were obtained. When a build up of fat/protein was noted on the electrode that greatly reduced its sensitivity to pH changes the probe was removed, wiped with ethanol, rinsed with distilled water, and replaced.

Rapid coating of the tip of the pH probe occurred particularly when titrating Farley's milk, and it was constantly necessary to clean it. For this reason, once a baseline and initial drop in pH had been recorded as usual, the probe was only dipped into the sample approximately every five minutes to obtain values.

Each sample was tested a minimum of three times.

Data analysis
The data from the recorder were downloaded on to an Apple Macintosh computer through an RS-232-C Interface (Novo Diagnostic Systems) and transferred to a spreadsheet (Microsoft Excel) for analysis. pH values were converted to H^+ concentration before analysis because the pH scale is logarithmic. The neutralisation capacity of each sample was calculated as the number of moles of acid required to return the pH to a baseline value.

IN VIVO STUDY
Patients
All infants aged less than 1 year and primarily on milk feeds referred to the Queen's Medical Centre, Nottingham for evaluation of suspected reflux were recruited for our study. All patients were admitted either because of problems such as failure to thrive, apnoeic attacks, excessive regurgitation, or inconsolable crying, were awaiting surgery, or were outpatients who were admitted specifically for oesophageal pH monitoring.

Ethical approval was obtained from the Queen's Medical Centre, Nottingham University Hospital and the NHS trust ethics committee. The parents/guardians of the babies involved were fully informed, both orally and in writing, as to the nature of the test, and gave consent before the study.

Equipment
The Flexilog 2000 ambulatory pH monitoring system (Oakfield Instruments, Oxford, UK) was used. This consisted of a dual channel, portable, digital data recorder and a nasogastric catheter, combining two antimony pH electrodes. A distance between the electrodes of 5 cm was chosen for this age group.

The electrodes were cleaned to remove oxidation and calibrated according to the manufacturer's instructions. The sampling rate was every six seconds for 24 hours.

Protocol
Each infant was fasted for at least four hours before the test and GOR treatment was stopped before and during the test.

The sterile catheter was passed transnasally and a nomogram was used to estimate the distance to the cardia, to situate the electrodes 2.5 cm on either side of it. The pH was checked to confirm correct positioning and then a chest radiograph was carried out to verify the position of the electrodes. The

Table 1 Composition of baby feeds used

Food	*Mass used (g)*	*Protein (g)*	*CHO (g)*	*Energy (kJ)*	*Fat (g)*	*Principal CHO*	*Protein source*
Premium	1.433	1.4	7.1	276	3.6 (MCT)	Lactose	Cows' milk
SMA Gold	1.5	1.5	7.2	271	3.6	Lactose	Whey based
Pepti-Junior	1.466	2.02	7.5	309	4.2 (MCT)	Glucose	Whey hydrosylate
Pregestimil	1.633	2.11	10.3	313	3.0 (MCT)	Glucose polymers	Casein hydrosylate
Prosobee	1.433	2.24	7.3	313	4.0 (LCT)	Glucose	Soya bean
Neocate	1.666	2.17	9	322	3.8	Glucose	Not whole protein based
Fruit juice	NA	Trace	6.6	113	Trace	Unknown	NA
Dioralyte	NA	None	None	None	None	NA	NA
Breast milk	NA	1.06	7.1	313	4.5	Lactose	Lactalbumin casein
Farley's	NA	1.85	7.2	301	4	Unknown	Whey based

CHO, carbohydrate; LCT, long chain triglyceride; MCT, medium chain triglyceride; NA, not available.

electrode was marked near to the nostril to allow correct repositioning if the probe became displaced. The electrode was secured to the infant's face using tape, and mittens were used to prevent the infant from removing the electrode. The reference electrode was attached to the infant's back using an electrocardiogram electrode pad. A diary card was completed, noting meal times, feed type, supine periods, and symptoms. Normal activities were resumed for the recording period, which lasted for approximately 24 hours.

Data analysis

On completion of monitoring, a post-calibration was performed and any drift since the start of the experiment was linearly corrected. Data were downloaded on to pH analysis software (Flexisoft II; Oakfield Instruments). Data were then transferred to a spreadsheet (Microsoft Excel) to calculate the following:

(1) The percentage time that oesophageal pH was < 4 for the total recording period[3]
(2) The time that both the oesophageal pH and the gastric pH were < 4, as a percentage of the time that the gastric pH was < 4. This measure evaluates the dependency of oesophageal pH on gastric pH; if it is 100%, then the oesophageal pH is always < 4 when the stomach pH is < 4; if it is zero, then the oesophageal pH is never < 4 when the stomach pH is < 4
(3) The percentage time that oesophageal pH was < 4 for the periods of time that gastric pH was > 4, again as a percentage of the time that gastric pH was > 4. This quantifies the occurrence of oesophageal acidity when the stomach pH is > 4
(4) The total exposure of the oesophagus to acid, calculated as the area under the H^+ time curve (H^+ min)
(5) The exposure of the oesophagus to acid during the period that gastric pH was < 4 (H^+ min), which quantifies the amount of acid reaching the oesophagus when the gastric pH is relatively low
(6) The exposure of the oesophagus to acid during the period that gastric pH was > 4 (H^+ min).

All calculations were performed using H^+ concentration rather than pH.

It is generally accepted that the oesophageal pH should be < 4 for 10% of the recording time for a clinical diagnosis of reflux.[4] In children, this was found to correlate most accurately with histological evidence of reflux (57% have histological changes above this value, but only 6% have such changes below this value). Consequently, we used this value to separate infants with reflux from those without. We then reassessed each patient taking into account the time for which the gastric pH was < 4.

Results

IN VITRO STUDY

Table 2 shows the neutralisation capacity of infant feed and varies from 0.85 (Dioralyte) to 2.92 (Pepti-junior) mM/10 ml milk. Breast milk had an intermediate value of 2.15 mM/10 ml.

Table 2 Neutralisation capacity of infant feeds

Test sample	*Sample pH*	*Neutralisation capacity (mM)*
Dioralyte	4.9	0.850
Fruit juice	4.0	1.552
Farley's	6.7	1.602
Premium	7.8	1.908
Breast milk	7.4	2.146
Neocate	6.1	2.156
Pregestimil	6.0	2.608
SMA Gold	6.9	2.678
Prosobee	6.9	2.775
Pepti-Junior	6.3	2.919

IN VIVO STUDY

A total of 35 babies was recruited and their average age was 4 months. The primary reasons for admission were persistent vomiting (16), apnoea (10), and refusing feeds (5). Other reasons were irritability, coughing during feeding, chest congestion, choking, breathing difficulties, and periods of distress. Complete sets of data were obtained from 30 infants.

The average gastric pH was ⩽ 4 for a mean (SEM) of 42.4% (4.9%) of the recording time; however, there was a wide range, from 1.7% to 98.8%. Figure 1 shows these data plotted against age. The mean (SEM) percentage time that oesophageal pH was < 4 for the total recording period was 6.89% (0.92%). When this was recalculated as a percentage of the time that the gastric pH was < 4, this value rose to 17.81% (2.46%) (fig 2). This was significantly different from that obtained using the standard method of scoring ($p < 0.0001$). Acid reflux was measured in the oesophagus for a mean (SEM) of only 1.9 (0.4%) of the total time when the gastric pH was > 4.

Similar trends were observed when the total exposure to acid (H^+ min) was calculated. The mean (SEM) total acid exposure to the oesophagus was 1.32 (0.41) H^+ min, with 81.03% (3.79%) of this exposure occurring when the gastric pH was < 4. Using the conventional parameter of oesophageal pH < 4 for 10% of the recording time, 11 of the 30 babies were diagnosed as having reflux. However, recalculation ignoring the time for which gastric pH was high doubled the figure to 22 of the 30 as having reflux. Of these additional infants, seven were persistent vomiters and four were having apnoeic attacks. This increased the level of positive scores from 19% to 63% for vomiting and 25% to 75% for infants with apnoea.

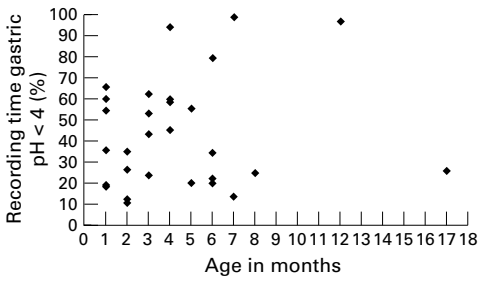

Figure 1 Comparison of the age of the babies in months against the percentage of recording time for which the gastric pH was < 4.

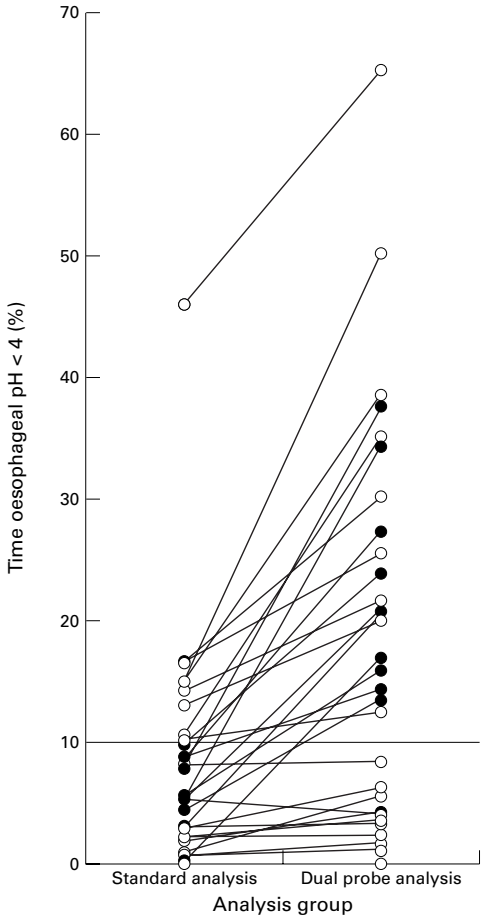

Figure 2 Comparison of the effect of using single probe and double probe methods on diagnosis. Points marked with solid dots indicate patients whose diagnosis was changed from negative to positive by the dual probe analysis.

Key messages

- Reflux of neutral feeds is not easily detectable by conventional pH monitoring procedures
- Conventional pH monitoring may severely underestimate the incidence of gastro-oesophageal reflux in babies
- A dual probe approach, which monitors gastric acid and oesophageal pH, leads to a significantly higher diagnosis rate

Discussion

Although it has been recognised that the buffering effect of formula can obscure the detection of reflux,[5 6] the magnitude of underdiagnosis in infants fed exclusively on formula milk has not been reported previously. A similar study that examined both gastric and oesophageal pH in children reported a change in diagnosis for 23% of the population, but this study was not limited to infants on milk feeds only.[7] Once children start solid foods, the frequency of feeding reduces, gradually becoming more "adult" in pattern.

Our study shows that the combined measurement of oesophageal and gastric pH permits a more accurate evaluation of the low acid and non-acid components of GOR, by revealing the extent of gastric subacidity in infants. The effect of prolonged periods of gastric subacidity has been shown in adults who have GOR.[8] In most of these patients, gastric pH was < 4 for a mean (SEM) of 89% (3%) of the of the recording time. However, the authors identified a subset of patients who had reflux symptoms, but were not positive for oesophageal acid reflux. In this group, gastric pH was only < 4 for a mean (SEM) of 28% (7%) of the recording time. Our study shows that babies on milk feeds have a gastric pH < 4 for a mean (SEM) of 42% (5%) of the recording time. This is approximately half that seen for the adults with positive oesophageal acid reflux. The time during which the gastric pH was < 4 varied greatly. This arises from an interplay of a multitude of factors, namely: the frequency of feeding; the volume of feed; the neutralisation capacity, composition, and energy content of the feed; and physiological factors, such as acid secretion and gastric emptying rates. To complicate matters further, there is no clear picture of the gastric emptying profiles of formula in infants with GOR. Some authors report that it is delayed,[9 10] whereas others report no difference in the age group under 3 years.[11] In our study, the few infants whose gastric pH was < 4 for most of the recording time all vomited after each feed during the study and had been admitted for persistent vomiting and choking.

We conclude that the current protocol for pH monitoring to assess GOR at Queen's Medical Centre might greatly underestimate the true incidence of GOR in neonates. Simultaneous measurement of gastric and oesophageal pH indicated the possibility of misdiagnosis in a large number of neonates. We suggest that GOR studies in neonates performed using a single probe should be assessed with considerable caution, and recommend that the pH of the gastric contents be taken into account when interpreting data.

Astra Zeneca had no involvement in this study.

1 Gomes H, Lallemand PH. Infant apnoea and gastroesophageal reflux. *Pediatr Radiol* 1992;**22**:8–11.
2 Evans DF, Haynes J, Jones JA, Stower MJ, Kapila L. Ambulatory esophageal pH monitoring in children as an indicator for surgery. *J Pediatr Surg* 1986;**21**:221–3.
3 Varty K, Evans D, Kapila L. Paediatric gastro-oesophageal reflux: prognostic indicators from pH monitoring. *Gut* 1993;**34**:1478–81.
4 Vandenplas Y, Franckx-Goossens A, Pipeleers-Marichal M, Derde MP, Sacre-Smits L. Area under pH 4: advantages of a new parameter in the interpretation of esophageal pH monitoring data in infants. *J Pediatr Gastroenterol Nutr* 1989;**9**:34–9.
5 Sutphen JL, Dillard VL. Dietary caloric density and osmolality influences GOR in infants. *Gastroenterology* 1989;**97**:601–4.
6 Rakowsky T. Simultaneous measurement of oesophageal and gastric pH values in formula-fed babies with gastro-oesophageal reflux. *Monatsschrift fur Kinderheilkunde* 1994;**142**:52–6.
7 Bocquet A, Schirrer J, Filipov P, Saade B, Noir A. Increasing sensitivity of oesophageal pHmetry by simultaneous monitoring of gastric pH: a study in 129 children. *Acta Endoscopica* 1992;**22**:337–45.
8 Ducrotte P, Touchais J, Weber J, Hecketsweiler P, Colin R, Denis P. Is simultaneous gastric pH monitoring useful to interpret 24-h oesophageal pH-metry? *Eur J Gastroenterol Hepatol* 1991;**3**:637–40.
9 Guillet J, Wynchank S, Christophe E, *et al*. Gastro-oesophageal reflux and gastric emptying of liquids in paediatric patients. *Int J Nucl Med Biol* 1984;**11**:254–58.
10 Baulieu F, Maurage C, Baulieu JL. A quantitative approach to gasto-oesophageal reflux in children. *Nucl Med Commun* 1984;**5**:689–95.
11 Di Lorenzo C, Piepsz A. Gastric emptying with gastro-oesophageal reflux. *Arch Dis Child* 1987;**62**:449–53.