Gastro-oesophageal reflux in preterm infants

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SUMMARY Gastro-oesophageal reflux in very low birthweight infants was studied using a new 1 mm monocrystalline antimony oesophageal pH electrode. Gastro-oesophageal reflux was detected in 30 (85%) subjects. The mean (SEM) number of episodes of reflux in 24 hours was 12.1 (2.1), and 3.2 (0.6) lasted over five minutes. The mean reflux index was 4.5 (1.0)%, and the longest episode 17.1 (4.6) 17.1. Reflux was unrelated to postconceptional age or to resting lower oesophageal sphincter pressure. The mean reflux index was low at rest before feeds, being 1.8 (0.6)%, and increased slightly after feeds (3.8 (1.0)%), but was significantly increased after nursing care to 16.4 (3.0)%, and while xanthines were being given (5.9 (1.6)%). A subgroup of seven infants with xanthine resistant apnoea had severe gastro-oesophageal reflux that was not clinically apparent (reflux index 27.4 (3.6)%). Successful treatment of the reflux (reflux index: 3.6 (1.2)%) was associated with cessation of the apnoea.

We conclude that gastro-oesophageal reflux is common, and is usually not clinically apparent, even when severe. It is important to consider gastro-oesophageal reflux in the differential diagnosis of xanthine resistant apnoea in preterm infants.

In preterm infants gastro-oesophageal reflux and subsequent pulmonary aspiration of gastric contents has been suggested as a complication of early feeding^{1 2} and has led to a cautious approach to the early introduction of enteral feeds. Gastro-oesophageal reflux has also been implicated in the pathogenesis of chronic respiratory problems such as bronchopulmonary dysplasia,³ and in the aetiology of apnoea and sudden infant death syndrome.⁴ In very low birthweight (VLBW) enterally fed, preterm infants receiving modern intensive care, however, the incidence, severity, and clinical importance of gastro-oesophageal reflux are not known.

We have therefore studied a group of VLBW preterm infants undergoing intensive care, to determine the overall prevalence of gastro-oesophageal reflux, the association with postconceptional age and with lower oesophageal sphincter pressure, and the effects of position, feeds, and nursing care. In addition, we studied the association between gastro-oesophageal reflux and apnoea in a separate group of VLBW infants with frequent attacks of apnoea.

Subjects and methods

VLBW PRETERM INFANTS RECEIVING INTENSIVE CARE

Fifty seven studies were carried out on 35 preterm

infants in the regional neonatal referral unit at Birmingham Maternity Hospital. Infants included were consecutive patients weighing less than 1500 g who met the inclusion criteria, and for whom informed parental consent could be obtained. Exclusion criteria included the presence of symptoms suggestive of gastro-oesophageal reflux such as vomiting or the aspiration of milk from the oropharynx. Infants were also excluded if they had evidence of other gastrointestinal disease, if they were severely ill, or if they had severe recurrent apnoea. Infants with mild apnoea who were having less than four episodes a day, and who did not require treatment were included (n=25); in 10 infants apnoeic episodes had not been noted before the study.

Median (range) birth weight was 1040 (720–1470) g; gestation 28 (25–33) weeks; and postnatal age 2 (0–7) weeks. Gestation was determined from antenatal history and the Dubowitz assessment.⁵ All but two infants were receiving milk feeds (median volume 132 ml/kg/day) reflecting a policy of early introduction of enteral feeds wherever possible. Among the infants studied there was a broad range of diagnoses typical of a neonatal intensive care unit: 31 studies were carried out on infants receiving supplementary oxygen, and six on infants receiving

assisted ventilation. Four infants has hyaline membrane disease, nine infants has chest infections, five had bronchopulmonary dysplasia, three were being treated for septicaemia, and eight were small for gestational age.

INFANTS WITH FREQUENT ATTACKS OF APNOEA

In the second investigation only infants with frequent apnoea were studied. Apnoea was defined as an episode of absent chest movement of greater than 20 seconds with or without cyanosis, or of bradycardia with cyanosis. Recovery followed stimulation with or without the administration of oxygen. 'Frequent apnoea' was defined as 12 or more such episodes in 24 hours.

Three subgroups were studied:

The first subgroup comprised six infants with frequent untreated attacks of apnoea. Three of these were studied before treatment was started. In the other three, frequent attacks of apnoea were associated with periventricular leucomalacia ($n=2$) or upper airways obstruction ($n=1$), and treatment with xanthine derivatives was considered inappropriate.

The second subgroup comprised eight infants with xanthine sensitive apnoea who had previously had frequent attacks of apnoea but, at the time of the study, were having less than three episodes a day during successful treatment with a xanthine. Xanthines used were theophylline (loading dose 7.5 mg/kg, and maintenance dose 3 mg/kg/day, which was adjusted to maintain serum concentrations at 13–20 mg/l), and caffeine (loading dose 50 mg/kg, and maintenance dose 12 mg/kg/day, which was adjusted to maintain serum concentrations at 28–40 mg/l).

The third subgroup comprised 13 infants with xanthine resistant apnoea. These infants had frequent attacks of apnoea that were unaffected by the administration of a xanthine and after full investigation had no evidence of central nervous system disorder, airways obstruction, or other primary cause for the apnoea.

The data from the infants with frequent attacks of apnoea were compared with those from the VLBW preterm infants receiving intensive care who had had no apnoeic episodes at all ($n=10$). None of the subgroups among the apnoeic babies differed significantly with respect to birth weight, gestation, age, or feeding. As in the VLBW preterm infants, none of them had clinical features of gastro-oesophageal reflux.

MEASUREMENT OF GASTRO-OESOPHAGEAL REFLUX

Intraoesophageal pH was monitored continuously for 24 hours using an intraluminal pH probe. A simultaneous record of heart rate was made from the neonatal monitor (Hewlett-Packard, type 78801).

pH probe

A new 1 mm monocrystalline antimony electrode (Monocrystant—infant) was developed in conjunction with Synectics Medical. The antimony electrode produced a corrosion potential (-53 mV/pH) proportional to the surrounding pH relative to a reference electrode.⁶ Although corrosion or oxidation of the surface of the crystal is minimised by cleavage of the crystal along a crystal plane,⁶ careful calibration of the electrode before and after studies was essential. This was carried out using non-phosphate buffers (Synectics Medical) at pH 7.0 and 1.0. Calibration was considered satisfactory and data accepted if the pH electrode gave a stable reading between 6.9 and 7.1 for 10 minutes in a buffer with a pH of 7.0, and also after immersion in a solution with a pH of 1.0, showing a recovery to pH >6.7 in less than 15 s when reimmersed in a solution with a pH of 7.

No consistent drift was noted, and when stability was tested in a buffer with a pH of 7 for 24 hours the maximum deviation from the pH of 7 was 0.2.

Antimony electrodes age as the surface of the antimony crystal becomes slowly corroded. Calibration remained satisfactory for between 3 and 17 (mean 8.3) days of use.

pH recording

A karaya gum electrocardiograph electrode (Arbo pink H28) was used as a skin reference and produced stable contact with neonatal skin.

The potential generated by the pH electrode was amplified by a patient isolated amplifier (Ormed pH unit 4990, in preamplifier housing MT4PX-48) and recorded on a chart recorder (Philips PM 8216).

Positioning the pH electrode

The 1 mm pH electrode was bonded to a medical grade PVC nasogastric tube (umbilical arterial catheter, 3.5 Charrière, external diameter 1.2 mm) with a solvent welding solution (Vynol glue) such that the nasogastric tube extended 5 cm beyond the tip of the pH probe. The tube had a single end opening, and was attached to a previously described manometric system⁷ continuously perfused at 3 ml/hour. This was used to determine the position of the high pressure zone of the lower oesophageal sphincter and the level of the diaphragm. The nasogastric tube was then advanced 3–4 cm below the diaphragm into the stomach, leaving the pH electrode in the lower oesophagus 1–2 cm above the sphincter. Radiography was not used. The manometric system was used at the end of each study to measure resting lower oesophageal sphincter pressure.⁷

FEEDS AND NURSING CARE

During the study the infants were fed through nasogastric tubes using a standard feeding regimen⁸ and no change was made in routine care. Timing of feeds, nursing care, and position changes were marked on the recordings using an event marker. Nursing care comprised chest physiotherapy, oropharyngeal or endotracheal suction, and nappy changing. Physiotherapy was performed by a nurse for a few minutes while the infant remained in the incubator. The procedure included turning the infant and was followed by oropharyngeal and endotracheal tube suction using a fine catheter. Whenever necessary the nappy was changed in the incubator and a clean nappy loosely applied. Infants were routinely positioned in three positions: prone, or right or left lateral.

ANALYSIS OF DATA

Gastro-oesophageal reflux was defined as a fall in intraoesophageal pH to less than 4 for more than 15 seconds.⁹ The following were recorded from the traces: the number of episodes in 24 hours; the number of episodes of more than five minutes duration in 24 hours; the longest single episode of reflux in minutes; and the reflux index, which was defined as the percentage of the observation period during which the pH was less than 4.

Table 1 Incidence of gastro-oesophageal reflux in 57 studies of 35 VLBW preterm infants receiving intensive care

	Mean (SEM)
No of episodes/24 hours	12.1 (2.1)
No of episodes lasting ≥ 5 min/24 hours	3.2 (0.6)
Reflux index (%)	4.5 (1.0)
Longest episode (min)	17.1 (4.6)

The effects of feeds and nursing care were determined by comparing gastro-oesophageal reflux in the 30 minute epoch preceding feeds or nursing care with the 30 minute epoch afterwards. The effect of position was evaluated by comparing the cumulative amount of reflux during four hour periods in each position.

Statistical analysis was by Student's *t* test. Values are expressed as mean (SEM) and, where comparisons are made, with standard error of the difference between the means (SE diff). The protocol was approved by the district research ethical committee, and informed consent obtained from the parents before each study.

Results

VLBW PRETERM INFANTS RECEIVING INTENSIVE CARE

Incidence of gastro-oesophageal reflux (table 1)

Despite the absence of clinical reflux, a mean of 12 episodes/24 hours was observed, although only three in each 24 hours lasted longer than five minutes. The mean reflux index was 4.5 (1.0)%, and 85% of recordings showed a reflux index of $>1\%$.

The amount of reflux did not correlate with either resting lower oesophageal sphincter pressure ($r=-0.04$), or with postconceptional age ($r=0.12$).

Effect of feeds, nursing care, and position (table 2)

At rest infants had little reflux (reflux index 1.8 (0.62)%), and there was a moderate, but not significant, increase after feeds (reflux index 3.8 (1.01)%, SE diff 1.2).

Physiotherapy and suction were associated with a pronounced increase in the amount of reflux (reflux index 16.4 (2.97)% SE diff 3.5, $p<0.01$). Nursing care was also associated with significant increases in the number of episodes (SE diff 0.23, $p<0.01$), and

Table 2 Comparison of gastro-oesophageal reflux in 30 minute epochs before and after feeds, nursing care, and nappy change. Results are expressed mean (SEM)

	No of episodes/30 minutes	No of episodes ≥ 5 minutes/30 minutes	Reflux index (%)	Longest episode (minutes)
30 minutes before feed or nursing care (n=481)	0.20 (0.06)	0.07 (0.03)	1.8 (0.6)	5.6 (2.0)
30 minutes after feed (n=308)	0.45 (0.16)	0.10 (0.05)	3.8 (1.0)	7.2 (1.8)
30 minutes after nursing care (n=158)	1.4* (0.20)	0.30* (0.06)	16.4* (3.0)	7.9 (1.3)
30 minutes after nappy change by mother (n=13)	1.7* (0.34)	0.48* (0.19)	27.0* (6.3)	8.6 (2.1)

* $p<0.001$ compared with value before feed or nursing care; n=number of 30 minute periods observed.

the number of episodes of longer than 5 minutes (SE diff 0.08 $p<0.01$). The event most likely to be associated with reflux was a nappy change performed by the infant's mother (reflux index 27.0 (6.3)%; SE diff 6.3, $p<0.001$) (table 2).

The prone and right lateral positions were associated with similar amounts of gastro-oesophageal reflux (reflux index 3.9 (1.2)%, and 3.5 (1.65)%, respectively; SE diff 2.0). There was a trend towards increased reflux in the left lateral position (reflux index 7.3 (2.8)%; SE diff 2.9), but this was not significant.

INFANTS WITH FREQUENT ATTACKS OF APONOEA

There was no significant difference between those patients with frequent attacks of apnoea (reflux index 3.1 (1.1)%, and the 10 VLBW preterm infants without apnoea (reflux index 2.4 (0.7)%, SE diff 1.3). These results did not, in fact, differ from the overall mean found for all the VLBW preterm infants (table 3).

Successful treatment of apnoea with a xanthine was associated with significant increase in both the reflux index (5.85 (1.6)%, SE diff 1.6, $p<0.05$) (table 3), and the mean longest episode ($p<0.01$).

Thirteen VLBW infants with xanthine resistant

Table 3 Reflux index in infants without apnoea, with frequent untreated attacks of apnoea, and with xanthine sensitive apnoea

	Mean (SEM)
No apnoea (n=10)	2.4 (0.7)
Frequent untreated attacks of apnoea (n=6)	3.1 (1.1)
Xanthine sensitive apnoea (n=8)	5.9 (1.6)*

* $p<0.05$ compared with group with no apnoea.

apnoea were studied. These infants did not differ from any of the other infants with respect to birth weight, gestation, postconceptional age, or feeding. The mean reflux index (16.5 (4.1)%) was raised compared with that of the VLBW preterm infants (SE diff 3.1, $p<0.01$). Inspection of the data, however, showed that there were two distinct subgroups of patients: though there was no difference in the frequency or severity of the attacks of apnoea in these two subgroups, six of the 13 had a reflux index within the observed range for VLBW infants receiving intensive care, (2.7 (0.9)%, SE diff 2.3), whereas the remaining seven infants had severe gastro-oesophageal reflux. The mean reflux index of

Figure Xanthine resistant apnoea: intervention study. (a) Reflux indices in individual subjects before and after antireflux treatment ($p<0.001$); (b) Number of apnoea attacks/24 hours: before diagnosis of reflux, and on first and second days after starting antireflux treatment ($p<0.01$).

Table 4 Xanthine resistant apnoea: intervention study. Results are expressed as mean (SEM); n=7

	No of episodes/24 hours	No of episodes ≥ 5 minutes/24 hours	Reflux index (%)	Longest episodes (minutes)
Before treatment, severe apnoea	48.9 (6.7)	18.4 (3.2)	27.4 (3.6)	35.0 (4.1)
After treatment for gastro-oesophageal reflux, no apnoea	10.9* (4.1)	2.9* (1.1)	3.6* (1.2)	24.0 (9.9)

*p<0.01 compared with value before treatment.

these seven (27.4 (3.6)%, SE diff 2.7) was grossly raised (figure). Other indices of reflux were also much higher than in the other study groups (table 4). In these infants, comparison of the heart rate record with the oesophageal pH trace failed to show a temporal association between episodes of apnoea and gastro-oesophageal reflux.

XANTHINE RESISTANT APNOEA: INTERVENTION STUDY

Antireflux management was instituted in the seven infants with high reflux indices: patients were nursed prone and tilted 30° head up, and, in the four patients with reflux indexes of over 20%, feeds were thickened (Carobel, Cow and Gate: 0.3–0.6 g/100 ml suspension). Successful control of reflux was associated with a pronounced reduction in the frequency of apnoea attacks over a period of 12–48 hours after the introduction of antireflux management (figure); the mean (SEM) number of apnoeic episodes in 24 hours was 19.4 (3.3) before treatment, and fell on the first day of treatment to 12.0 (2.8) (SE diff 4.3), and on the second day of treatment to 3.6 (1.0), (SE diff 3.4, p<0.01). This clinical improvement was maintained when the xanthine treatment was withdrawn. pH studies were repeated between two and 11 days after the onset of antireflux measures, while infants were still receiving treatment. The mean reflux index had fallen from 27.4 (3.6)% to 3.6 (1.2)%, (SE diff 3.8, p<0.001), and there was also a highly significant reduction in the number of episodes and the number of episodes lasting longer than 5 minutes (SE diff 3.4, p<0.01); the reduction in the mean longest episode was not significant (table 4, figure).

Consent was obtained to study three of the seven infants with reflux again at between 38 and 43 weeks' postconceptional age (six to 11 weeks after the study after treatment). The studies were performed over 24 hours during temporary withdrawal of feed thickeners. Reflux indices in all three were still abnormal (mean reflux index 15.2 (1.2)%). All infants remained on feed thickeners until weaned.

Discussion

We have shown that clinically undetectable gastro-oesophageal reflux is common among preterm infants. Reflux is increased by nursing procedures and by xanthines, and there is a strong association between apnoea and reflux in the small group of infants with xanthine resistant apnoea, who responded well to antireflux measures.

Of the various methods available, continuous intraoesophageal pH measurement is now well established as the single most sensitive method of monitoring gastro-oesophageal reflux.^{10 11} Since the development of the 1 mm pH electrode, which permitted easy passage of the combined probe and nasogastric tube, it was possible to use this technique even in infants weighing under 1000 g. The technique is well suited to use in the intensive care unit, as the infants' routine care and feeding regimens need not be disturbed.

Gastro-oesophageal reflux is more common in asymptomatic, preterm infants than has previously been reported in infants born at full term,¹¹ or older children.^{12 13} In our group of VLBW preterm infants receiving intensive care, however, there were no discernible symptoms associated with gastro-oesophageal reflux, nor did it change within the range of maturation studied.

We have previously shown that lower oesophageal sphincter pressure rises with increasing maturity,⁷ and yet no correlation was found between gastro-oesophageal reflux and postconceptional age. In common with previous studies in adults we also failed to show a correlation between resting lower oesophageal sphincter pressure and gastro-oesophageal reflux.¹⁴ It is possible, therefore, that inappropriate relaxation of the sphincter is the mechanism of reflux in these babies. We cannot, however, entirely rule out the possibility that the presence of a nasogastric tube promotes reflux.

We found only a small increase in reflux index

after feeds above the low values seen at rest. Postprandial reflux is well recognised,¹² and the smallness of the increase seen here may be caused, at least in part, by the buffering of gastric acidity by the feed. In well, preterm infants on 120–240 ml/kg/day (taken as three hourly formula feeds) intragastric pH rises above pH 4 for up to 90 minutes after a feed.¹⁵ In our study infants were fed smaller volumes as hourly bolus feeds. We have measured intragastric pH in eight such infants on 90 ml/kg/day, and found that buffering to over pH 4 occurred after 28% of feeds, and lasted up to 25 minutes. Clearly therefore, our observations may underestimate the importance of postprandial reflux.

There was, however, a strong temporal association between gastro-oesophageal reflux and nursing care. Though oropharyngeal or endotracheal suction might provoke gastro-oesophageal reflux through stimulation of the retropharynx, it was also associated with other nursing procedures. It was most pronounced after nappy changes performed by the infants' mothers, who presumably had less expertise than that of the nurses.

Though there was some increase in the reflux index and the number of episodes lasting longer than five minutes when the babies were nursed in the left lateral position, there is no evidence to recommend any change in the three positions used for routine care. The supine position was avoided because of its well recognised association with gastro-oesophageal reflux.¹⁶

The putative association between apnoea and gastro-oesophageal reflux remains contentious.^{3 17} We found that among infants who had frequent attacks of apnoea all indices of reflux were marginally higher than in those infants who had no apnoea. This difference was not significant. In contrast, however, in those infants whose apnoea had been successfully treated with a xanthine, even though the frequency of attacks was reduced, significantly higher indices of reflux were observed than in non-apnoeic subjects. These observations are consistent with previous studies in which xanthines have been shown to increase gastro-oesophageal reflux in infancy¹⁸ and to reduce lower oesophageal sphincter pressure in adults.¹⁹

Our data strongly support the hypothesis that in a subgroup of infants with apnoea, there is a close association with gastro-oesophageal reflux. Routine investigation of attacks of apnoea in seven infants showed no cause for the apnoea but, unlike infants with primary apnoea, these infants did not respond to xanthine derivatives. There was, however, a dramatic response to antireflux measures. Short term follow up of these infants suggests that they continue to reflux, but that (in common with most

infants with gastro-oesophageal reflux) this tendency resolves with increasing age.

The mechanism by which reflux associated apnoea is mediated is unknown. Authors disagree about whether episodes of reflux and apnoea occur simultaneously.^{3 17 20 21} In our study reflux and apnoea were not simultaneous. We also noted that following the introduction of treatment for gastro-oesophageal reflux, apnoea attacks did not stop until 12–48 hours later (figure). This suggests that a vagally mediated reflex secondary to stimulation of laryngeal chemoreceptors by regurgitated milk^{22 23} is unlikely to be important here. It is possible, however, that apnoea associated with severe gastro-oesophageal reflux is mediated through a vagovagal reflex secondary to oesophagitis and abnormal oesophageal motility,^{24 25} both of which are recognised complications of reflux.^{3 26 27}

What are the implications of these findings for the management of xanthine resistant apnoea in preterm infants receiving intensive care? The performance of reflux studies in VLBW infants is, and will probably remain, essentially a research procedure. A pragmatic approach may therefore be adopted. On finding a preterm infant with xanthine resistant apnoea in the absence of other demonstrable aetiology a trial of antireflux treatment may be started. If successful in controlling apnoea, xanthines (which may aggravate reflux) could then be withdrawn.

In conclusion, we have found that gastro-oesophageal reflux is common and that, even when severe, it may not be immediately apparent clinically. The evidence for the association with nursing care may have implications that merit discussion with nursing colleagues. Reflux was not generally increased in infants with apnoea, but our data suggest a causative association in a subgroup of infants with xanthine resistant apnoea. Clearly the role of reflux in the aetiology of neonatal apnoea deserves further evaluation, and highlights the importance of studies of gastro-oesophageal reflux in this age group.

Dr SJ Newell was sponsored by the National Fund for Research into Crippling Diseases (Action Research) and gratefully acknowledges their support. We thank Synthetics Medical for providing the antimony pH electrodes, Mr GW Hollins and Mr PH Williams of the medical physics department of the Birmingham Maternity Hospital for their technical expertise, and the medical and nursing staff of the neonatal unit for their cooperation.

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Accepted 19 December 1988