Bronchial hypersecretion in preterm neonates

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SUMMARY During an 18-month period, 11 preterm infants with birthweights between 700 and 1560 g (mean 1.2 kg) developed excessive tracheobronchial secretions during intensive care. No single obstetric factor was incriminated. Copious, viscous, tracheobronchial secretions were noted at about 5 days during mechanical ventilation via endotracheal tube causing recurrent segmental collapse, hypoxia, and hypercapnia (median peak PCO_2 13.5 kPa). All infants were treated with frequent bronchial lavages and continued intermittent positive pressure ventilation, together with high concentrations of oxygen. No infant died, but morbidity was high. Tracheostomy was performed on 2 infants (one at age 3 months, because of severe croup) and 2 others had clinical or physiological evidence of upper airways narrowing. Follow-up studies showed that this group had more problems of airways obstruction throughout the first year of life as well as increased lung stiffness. The hypersecretion group showed a higher incidence of chronic lung disease. Likely aetiological factors were sought. Contamination of the mechanical ventilation equipment by detergent and activated glutaraldehyde was found; this could have been a contributory factor.

Although recurrent bronchial obstruction and endotracheal tube blockage are common during neonatal intensive care, there is no comprehensive report of the problem. We report here the clinical features, management, and outcome of 11 very low birthweight infants who all suffered from the effects of excessive tracheobronchial secretions.

Clinical features

During an 18-month period, 11 infants of very low birthweight (the largest weighed 1560 g) who were admitted to the neonatal intensive care unit, Hammersmith Hospital, developed a similar pattern of recurrent airways obstruction associated with apparently excessive tracheobronchial secretions, necessitating repeated bronchial lavage and mechanical ventilation. They were compared with a control group of 11 infants matched only by birthweight and the need for mechanical ventilation in the neonatal period. Mechanical ventilation was instituted when lesser forms of respiratory support had failed to prevent severe hypoxia, hypercapnia, or persistent apnoea. Patients and controls were studied in detail only after recovery from their acute phase, so this report deals only with survivors, and is not an epidemiological study of tracheobronchial hypersecretion in the newborn. There were no obvious obstetric difficulties in the study group, nor did the clinical features of the study and control groups differ significantly (Table 1). In both the study

and control groups, 10 of the 11 infants were white and the remaining infant was coloured (mixed race).

The technique of mechanical ventilation followed closely the well established principles developed in this department,¹ using a pressure-limited, time-cycled ventilator (Vickers Neovent 90) and humidifier (Vickers). Size 2.5 to 3.5 mm shouldered oro-tracheal tubes (Portex) were used whenever endotracheal intubation was needed. Regular tracheal toilet (after instillation of 1 ml physiological saline when necessary) was performed at 1-2 hourly intervals. Characteristically, on about day 5 the secretions became copious and thereafter continued for about 2 weeks. All the affected infants required endotracheal intubation and mechanical ventilation before age 8 hours. The earliest sign of hypersecretion was the aspiration of increasing amounts of mucus on suctioning of the endotracheal tube. This was followed by recurrent blockage of the endotracheal tube and pulmonary airways, manifest by pulmonary segmental collapse and consolidation. Increasing hypoxia, hypercapnia, and acidosis developed during these episodes of obstruction. As a result, the median maximum arterial PCO_2 was 13.5 kPa (101 mmHg) in the study group, and 9.3 kPa (70 mmHg) in the control patients. The mean duration of oxygen requirement for the hypersecretion group was 2 weeks longer than that of the control group but the groups were well matched for duration of mechanical ventilation (Table 1).

Table 1 Clinical details (mean values and range)

	Control	Hypersecretion
Male:female	9:2	10:1
Birthweight (kg)	1.15 (0.91-1.35)	1.2 (0.7-1.56)
Gestational age (weeks)	28.6 (26-32)	28.6 (27-30)
Duration of oxygen therapy (days)	28 (6-90)	37 (6-70)
Mechanical ventilation (days)	11 (1-47)	10 (1-19)
Apgar score (mean)		
1 min	4.3	5.2
5 min	7.4	6.3
Main condition leading to mechanical ventilation (number of infants)		
Respiratory distress syndrome	5	4
Apnoea and respiratory distress syndrome	5	3
Apnoea	1	4
Hypersecretion		
Age at onset (days)		4.6 (2-8)
Duration of need for bronchial lavage (days)		16 (6-30)

Management of recurrent tracheobronchial obstruction

Whenever the accumulation of excessive tracheobronchial secretions produced clinical deterioration as manifest by progressive hypoxia in intubated patients, or by progressive distress and hypercapnia in patients breathing spontaneously, or by persistent segmental collapse on chest x-ray film, bronchial lavages were started and repeated as necessary. The procedure varied little between different operators. Basically, the infant was extubated, if previously intubated, with tracheal suction, then hand ventilated via face mask with 100% oxygen for about 30 seconds or until the transcutaneous oxygen monitor or umbilical artery oxygen electrode indicated a significant improvement in the PO_2 . One millilitre of physiological saline was then instilled through the vocal cords under direct vision. The infant was then quickly tipped and brief chest percussion performed followed by suction through the vocal cords, intubation, and hand ventilation until a satisfactory PO_2 had been achieved. Occasionally, the infant was not extubated, and the lavage performed through the endotracheal tube. The infants in the study group received many lavages, some repeatedly for several days (range 4 to >30 lavages), until either the quantity of secretions had diminished or the clinical problems caused by excessive secretions had resolved. The need for bronchial lavages was, in fact, the necessary criterion for admission to the study group.

Investigations

Secretions. Attempts were made to measure the absolute amount of secretions. As there were varying amounts of bubbles in the fluid, volumetric

measurement was not appropriate. The stickiness of the fluid made suction using a dry catheter ineffective, while wetting the suction catheter automatically invalidated the weight of any fluid collected. Collection of uncontaminated specimen proved impossible. Bacteriological studies were done on all the infants including culture of the secretions and the tips of endotracheal tubes. No virological studies were routinely done.

Pulmonary function. Lung function tests were performed in a whole body plethymograph. The first test was at the time of discharge from the neonatal intensive care unit, and subsequent tests 4-6 and 10-12 months later. Infants were sedated with chloral hydrate 30-50 mg/kg after a feed using techniques described elsewhere in detail.² The following parameters were determined: thoracic gas volume, airways resistance, pulmonary resistance, dynamic compliance. The expected normal values were derived from a previous study on more than 200 normal infants who did not have respiratory distress, using identical methods. The study was approved by the Hammersmith Hospital Ethics Committee.

Clinical follow-up. At 6-monthly follow-up appointments, clinical and, if indicated, radiological evaluations were carried out.

Toxicology. Because of the suspicion on a previous occasion that contamination of the ventilator circuit might be responsible, the following investigations were performed.

Four humidifiers (Vickers Model 90) were obtained randomly from ward stock having undergone routine sterilisation with alkalised glutaraldehyde, and were tested for residual glutaraldehyde using an air flow of 3 l/min, by the procedure of Varpela *et al.*³ The humidifiers, had previously been routinely dismantled and soaked in activated glutaraldehyde for 10 minutes, then rinsed by passing through 2 containers of distilled water before being drip dried.

Detergent detection was performed on 6 sets of ventilator tubing. The ventilator tubing had been routinely washed in hot water with detergent, then rinsed with tap water before autoclaving. In order to detect residual detergent, each set of tubes was rinsed with 50 ml of distilled water. This solution was then shaken with methyl phosphate (1%, pH 10.0) and the surfactant-dye complex extracted into chloroform. The blue-coloured solution was compared with standard solutions containing 0-10 ppm active detergent.

Results

Secretions. The secretions were thick and sticky in all but 2 cases which were watery. Visual examination of the secretions showed that the quantity of the secretions was more than sufficient to block an infant's endotracheal tube easily. No one single organism was common to the group. All 11 patients were already on antibiotics well before the onset of hypersecretion for either suspected or proved sepsis, so the significance of these isolates is unclear.

Clinical. Two infants from the hypersecretion group required tracheostomies. One was performed at age 1 month to aid bronchial toilet so that he could be weaned off the endotracheal tube. At the time, he had no clinically detectable upper airways obstruction. This infant still had excessive secretions at age 3 months. The other tracheostomy was fashioned at another hospital for severe acute laryngotracheo-bronchitis at age 3 months. Chronic lung disease, defined by radiological evidence of bronchopulmonary dysplasia grade IV⁴ or by more than 4 weeks of increased oxygen requirement, was more often present in the hypersecretion group (Table 2).

Two infants from the study group and 2 from the control group required readmission to hospital during the first year for acute lower respiratory tract infections. However, the interpretation of these figures must take into account the anxiety engendered by preterm infants during their entire infancy.

Lung function. Although all the patients (with the exception of the one with the tracheostomy) were examined at age 1–2 months, because of non-compliance only half of the infants were studied at about 10–12 months.

Lung volumes during the first year of life were similar in both groups (Fig. 1). Comparison of their regression lines showed that the two groups were not significantly different, nor were they significantly different from the normal control population ($P>0.05$). However, when individuals were examined, 4 infants from the hypersecretion group and 3 from the control group had low volumes during the latter part of the first year (Fig. 1).

Airways conductance, related to lung volume (Fig. 2), was low in both groups during the

whole of the first year suggesting persistent airways narrowing. In addition, 2 infants from the hypersecretion group had tracheostomies, while 2 others had stridor and plethysmographic evidence of upper airways obstruction as suggested by disproportionately raised airways resistance during inspiration.

Both groups had diminished compliance (stiff lungs) during the first few months after the intensive care period (Fig. 3). During the latter half of the first year, the dynamic compliance appeared to become normal more rapidly in the control group than in the hypersecretion group.

Toxicology. All 4 humidifiers were contaminated with glutaraldehyde, liberated at a mean rate of 19 $\mu\text{g}/\text{hour}$ by the test procedure, during the first

Fig. 1 Relationship between thoracic gas volume (TGV) and body weight. Shaded area represents 95% confidence limits for normal infants.

Fig. 2 Relationship between airways conductance and thoracic gas volume. Shaded area represents 95% confidence limits for normal infants.

Table 2 Long-term clinical outcome

	Control group	Hypersecretion
Readmission with acute lower respiratory tract infection	2	2
Tracheostomy	0	2
Chronic lung disease*	4	7

*See text.

Fig. 3 Relationship between dynamic compliance and thoracic gas volume. Shaded area represents 95% confidence limits for normal infants.

5 hours. Thereafter, little more was released. With a gas flow of 3 l/min through the humidifiers, this produced a mean gas concentration of $0.11 \mu\text{g/l}$ during the first 5 hours. The amount released from the worst contaminated humidifier was up to $33 \mu\text{g/hour}$ for a 2-hour period.

All 6 sets of ventilator tubing showed the presence of significant amounts of detergent in the wash solution, with 5 of the solutions exceeding 10 ppm detergent. The detergent contamination of the tubing was found to be eliminated by meticulous rinsing.

Discussion

The purpose of this report is to call attention to a distinct clinical entity which affects some very low birthweight infants while receiving mechanical ventilation. During the 18-month study period, clinically significant tracheobronchial hypersecretion affected at least 8% of such babies admitted to Hammersmith Hospital neonatal intensive care unit, or at least 16% of infants of very low birthweight receiving mechanical ventilation. The syndrome required the drastic measure of repeated bronchial lavage, and led to significant long-term morbidity.

Mucus is essential to carry dust, bacteria, and irritants out of the lungs by ciliary action. In addition, it prevents damage to the airways epithelium. Hypersecretion is due to secretion out-stripping removal or failure of mucus clearance. To

date there has been no study to measure the normal volume of tracheobronchial secretions in infancy. In the healthy infant, the secretions are wafted up the airways into the pharynx and then swallowed. Data from the only adult study estimated a daily output of 10-15 ml.⁵ Estimates have been extrapolated from results of animal experiments, but the figures varied widely. The great difference in normal ranges confirms the difficulty in collecting bronchial secretions. The lack of a standardised collection method means that each study results in the collection of different types of fluid.⁶

We propose a scheme which summarises some of the possible aetiological factors and the acute and long-term consequences of tracheobronchial hypersecretion (Fig. 4). It is possible that the procedure of bronchial lavage may be a major irritant leading to the persistence of the syndrome. Repeated intubation and tracheal suction almost certainly contributed to the upper airways obstruction of the hypersecretion infants. However, there seems to be no alternative to the very effective technique of bronchial lavage, until hypersecretion and its complications can be prevented.

The fact that only very low birthweight babies were affected suggests that this is the susceptible population. The small size of these infants' airways and the small endotracheal tubes used make blockage more likely. Their airways may be particularly sensitive to insults. Perhaps the endotracheal tube or the suction catheter mechanically irritated the upper airways.^{7,8} The tubes used were polyvinyl tubes (Portex). It is unlikely that any plasticiser would elute from these fairly firm tubes. The ventilators used were pressure limited, time cycled, constant flow models (Vickers Neovent 90). The mechanical ventilation system required a

Fig. 4 Scheme of possible aetiological factors in tracheobronchial hypersecretion.

multitude of tubes. It is not inconceivable that some of these tubes have been perished, although not visually obvious, or worse they may have released polyvinyl chloride plasticiser, a known tissue toxin, after repeat autoclaving.

We have shown that despite rigorous washing, the ventilator tubing contained traces of detergent and that the humidifiers had tracers of activated glutaraldehyde (Cidex). How significant these contaminants are in neonatal intensive care may never be known as no ethical experiments can be conducted to obtain direct evidence. The concentration of glutaraldehyde was similar to, although generally lower than that observed by Varpela *et al.*³ using different makes of equipment and prolonged sterilisation times. They established that mice could be kept without harm for 24 hours in air containing glutaraldehyde 33 µg/l and therefore concluded that glutaraldehyde sterilisation was safe. The variation that we observed in amounts of glutaraldehyde liberated from the humidifiers may reflect variation in length of exposure to it, length of time since sterilisation and efficiency, or rinsing after sterilisation.³

Activated glutaraldehyde is chemically similar to formaldehyde. Like the latter, it is a potent respiratory tract irritant. The effect of low concentrations (10 ppm) formaldehyde on the respiration of guinea-pigs has been studied.⁹

It is not inconceivable that even minute traces of activated glutaraldehyde left in the humidifiers after rinsing may be sufficient to irritate the lungs during mechanical ventilation, especially if a newly sterilised ventilator circuit and humidifier are used each day. Whether the small amount of activated glutaraldehyde found in our random sample of humidifiers was significant is unclear. However, if it is possible to leave detectable amounts in the equipment regularly, it follows that mistakes may be made in which larger amounts of contaminants are left behind. It is likely that some form of chronic irritation is the cause of the hypersecretion. The latent period of a few days before the onset further supports this hypothesis.

In older subjects and experimental animals, bronchial hypersecretion is a common accompaniment of airways inflammation caused by viruses, bacteria, allergens, or toxic agents. The mechanism is unknown.¹⁰ Of the many organisms isolated from the study group reported here, none was common to all the patients. It seems unlikely that a specific bacterial infection was causal; more probably, bacterial growth was a secondary effect of airways damage. Virological studies were not done routinely in our study.

The significantly prolonged oxygen requirement, and the upper airways stenosis together support the

fact that hypersecretion and its complications had a significant morbidity during infancy. The lack of mortality may be due to preselection, since only infants who survived several days on the ventilator developed hypersecretion, and only those who survived the neonatal period were studied.

Several previous studies of pulmonary function have shown significant abnormalities in the survivors of neonatal mechanical ventilation. Serial measurements of functional residual capacity and dynamic compliance performed by Bryan *et al.*¹¹ during the first year of life of such infants showed that the initially decreased forced vital capacity returned to normal by 2–4 months. Our measurements of lung volume showed no difference between the hypersecretion group and the control group. Three infants from each of these two groups had low lung volumes during the latter part of their first year. The significance of this finding is unclear. We would suggest that these few infants may have had small lungs at birth, an abnormality which might have contributed to their neonatal lung disease, and hence their need for mechanical ventilation. Those infants with large volumes found immediately after the intensive care period may have had 'gas trapping' due to airways disease. Dynamic compliance (a measure of lung 'stiffness') remained significantly lower than normal, in both the study and control groups, with recovery occurring towards the latter half of the year. However, it must be borne in mind that the dynamic compliance measured in the presence of airways disease is a reflection not only of lung stiffness, but is also affected by airways disease. Although not physiologically 'pure', it is probably a satisfactory functional measurement. Stocks and Godfrey,¹² measuring the lung function in 11 infants who required intermittent positive pressure ventilation, showed that by 7 months airways resistance was significantly increased when compared with a nonventilated group. They suggested that trauma to the airways occurred during ventilation, interfering with airways growth. Our results showed that airways conductance (the reciprocal of airways resistance) remained low throughout the first year of life, the hypersecretion group being more severely affected than the control group.

The subject of tracheobronchial secretion in the newborn has been neglected, despite its clinical importance. The presence of potentially toxic contaminants in scrupulously cared-for equipment serves as a warning, although proof of any relationship between contaminants and lung disease is lacking. We can only speculate on the long-term prognosis. The work of others has shown that neonatal physiological disturbances may persist into later childhood.¹³ It would seem possible that the

infants who suffered neonatal pulmonary hypersecretion may never achieve normal lung function.

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