Effect of salbutamol on oxygen saturation in bronchiolitis

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Abstract
Inhaled sympathomimetic agents are often used in bronchiolitis with little objective evidence of benefit. The arterial oxygen saturation (Sao2) reflects the adequacy of ventilation-perfusion balance. The aim of the current study was to determine the effect of inhaled salbutamol on Sao2. In a randomised, double blind study, 21 infants, admitted with bronchiolitis positive for respiratory syncytial virus, had continuous Sao2 measurements made before and after nebulised salbutamol or placebo. Sao2 was recorded over 30 minutes for a baseline, then during the 10 minutes of first nebulisation with either salbutamol or saline, then over 30 minutes after nebulisation, the 10 minutes of second nebulisation with the alternate regime, and another 30 minutes after this second nebulisation. Desaturation occurred after salbutamol and saline nebulisation. The fall in Sao2 with salbutamol was seen whether infants received it as the first or second nebulisation. The fall in Sao2 after saline was seen when given first, but not when given after salbutamol. The decrease in Sao2 was greater and more prolonged with salbutamol than with saline. Routine nebulised aerosol sympathomimetic treatment during acute bronchiolitis cannot be recommended.

Acute bronchiolitis in infants is a common cause of hospitalisation. The use of bronchodilators in respiratory viral bronchiolitis has been controversial.1-3 Studies during the acute and the recovery phase of bronchiolitis have shown variable change in respiratory resistance and work of breathing with some demonstrating increased hypoxia after a single dose of nebulised sympathomimetic.1-24 Improved conductance in some infants has been reported.9 Conflicting results from the limited measurements possible in this young age group and entrenched preconceptions still lead to uncertainty about the role of bronchodilators in the treatment of acute bronchiolitis.

Arterial oxygen saturation (Sao2) is the most relevant outcome measurement of the adequacy of ventilation and ventilation-perfusion balance. We measured the effect of aerosol sympathomimetics on continuous Sao2 measurements in infants with acute viral bronchiolitis.

Subjects and methods
SUBJECTS
Children admitted with cough and wheeze due to acute bronchiolitis were entered into the study within five days of admission. All children had no prior history of respiratory symptoms, the clinical findings of hyperinflation with wheeze and crackles on auscultation, and respiratory syncytial virus isolated by immunofluorescence of a postnasal aspirate. Severely ill children and those with associated chronic disabilities were excluded. Approval was obtained from the hospital’s medical ethics committee and parental consent was obtained. The children were studied while quiet without sedation.

We studied 21 infants; there were 11 boys and 10 girls with a mean age of 3 months (range 3 weeks–6 months) and mean weight 5.6 kg (range 3.6–6 kg). Fifteen were breast fed and 14 had a history of parental smoking. None had a history of asthma in first degree relatives. Three of the children were receiving supplemental oxygen.

VARIABLES
Sao2 was measured using a pulse oximeter (Nellcor N200E) with finger sensor attached to the patient and the output recorded on a chart recorder. Electrocardiogram leads were applied to check the heart rate and to detect arrhythmias. Heart rate, an electrocardiogram, and Sao2 were monitored continuously on the chart recorder paper. Observations were noted of movement, crying, and coughing throughout the 110 minutes. In those receiving supplemental oxygen, oxygen was continued in the same inspired concentration as before the study.

PROTOCOL
Subjects were studied using a double blind, random allocation, crossover design. Continuous Sao2 measurements were made over 110 minutes before and after nebulised salbutamol (2.5 mg/2 ml) or placebo (2 ml normal saline). Measurements were made during 30 minutes baseline, 10 minutes of first nebulisation, 30 minutes observation, 10 minutes of second nebulisation, and 30 minutes observation. Nebulisations were given using an AirLife jet nebuliser run from a compressed gas supply with a flow of 6 l/minute. For the three patients on oxygen, the concentration of oxygen was checked with an oxygen analyser (Teldyn), and maintained at the prestudy level using a Bird oxygen blender which could adjust the oxygen mixture and maintain a flow of 6 l/minute.

DATA ANALYSIS
The Sao2 tracing was analysed using a digitising...
graphic tablet and a morphometric program on an Apple E computer. The average Sao₂ for each minute was determined from the graph using area under the curves for each minute. The mean Sao₂ for baseline was obtained over the first 30 minutes. The means of the 10 minute nebulisation period and mean of 5 minutes epochs after nebulisation for each patient were taken. Readings beyond 25 minutes after the second nebulisation could not be analysed due to interference from excessive movement in the majority of patients.

The results of the patients first given salbutamol or saline were analysed with a two way analysis of variance and the significance of change in desaturation from baseline determined with Dunnett's q test. The results of patients given salbutamol as the second nebulising solution were analysed with a one way repeated measure analysis of variance. No further statistical analysis was performed on patients receiving saline second as there was some persistent effect of salbutamol used as the first nebulising solution.

The periods of maximum desaturation from baseline, the times to reach maximum desaturation, and the times taken for recovery to baseline saturation for each group of patients were studied using a Kruskal-Wallis test. The differences between groups were analysed with χ² or Mann-Whitney non-parametric test where appropriate.

**Results**

For the 13 patients receiving salbutamol first there was a desaturation from mean baseline percent Sao₂ of 96.4 and 96.6 (during nebulisation) to 95.0, 95.0, 95.3, 95.4, and 95.4 at each five minute epoch after nebulisation (fig 1). A most significant decrease occurred five and 10 minutes after salbutamol nebulisation (p<0.05). After saline as the second nebulisation, there was no further desaturation with an Sao₂ of 96.1 during nebulisation to 96.2, 96.5, 96.4, and 96.8 after nebulisation.

The eight patients receiving saline first also showed desaturation from a baseline Sao₂ of 97.2 and 96.8 (during nebulisation) to 96.3, 97.6, 97.5, and 97.5 for each five minute epoch after nebulisation, a significant drop being recorded five minutes after saline nebulisation (fig 2). However, the drop in Sao₂ was again more noticeable after salbutamol given as the second nebulisation, with Sao₂ of 97.4 during nebulisation and levels of 97.0, 95.9, 95.6, and 95.9 for each five minute epoch after nebulisation. A significant drop was seen 10 and 15 minutes after nebulisation.

Eleven of the 13 patients given salbutamol first had a desaturation from baseline after salbutamol. All eight given salbutamol second desaturated after this nebulisation. The maximum fall in Sao₂ from baseline was greater in those who received salbutamol first and those who received salbutamol after saline than those who received saline first (fig 3). Although there was no significant difference between groups for the median maximum falls in Sao₂ after the first nebulisation, nine of 13 had a maximum fall in Sao₂ greater than 4% after salbutamol as the first nebulisation compared with two of eight after saline as the first nebulisation (p<0.05).

**Figure 1** Sao₂ after an initial salbutamol nebulisation with a saline nebulisation after 30 minutes; * significant decrease, p<0.05.

**Figure 2** Sao₂ after an initial saline nebulisation with a salbutamol nebulisation after 30 minutes; * significant decrease, p<0.05.

**Figure 3** Maximum change in Sao₂ after saline nebulisation, salbutamol nebulisation, and salbutamol nebulisation 30 minutes after a previous saline nebulisation. Medians shown.
Four of the eight who had salbutamol as the second nebulisation showed a maximum fall in Sao2 greater than 4%. Median time to reach maximal desaturation after the first nebulisation was not significantly different between the salbutamol and saline groups (9–10 minutes and five minutes respectively).

The 11 patients given salbutamol who desaturated took a median of 12 minutes to recover while the other eight patients given saline who desaturated took five minutes to recover (fig 4). The time required for patients given salbutamol to recover was significantly longer (p<0.05).

Discussion

This study has demonstrated significant falls in Sao2 in infants with mild to moderate bronchiolitis given nebulisations of either salbutamol or saline with salbutamol having a more profound effect. Previous studies reporting the effect of bronchodilators in infants with bronchiolitis have used clinical scores or lung function measurements as outcome measures.5 6 9 13 21 Most have shown no improvement and some have reported deterioration in lung function after bronchodilator.7 20 21 Soto et al found increased conductance in about 30% but the clinical significance was uncertain.8 Reynolds measured arterial blood gas tensions but repeated measures could not be taken.22 Some have argued that measurements used have not been appropriate to document the potential benefit that is sometimes clinically apparent. We reasoned that Sao2 is the clinically significant outcome measure of the adequacy of ventilation and perfusion in this condition and that oximetry is a useful non-invasive method to document the effect of bronchodilators on Sao2. We have therefore used oximetry to measure the response to nebulised salbutamol over 30 minutes.

The study was a randomised, double blind, crossover design where patients acted as their own control. Chloral hydrate has been used in previous studies.7 8 13 14 21 As desaturation may occur with sedation in moderately sick infants with bronchiolitis no sedation was used in this study. Although some infants had coughing spells, they were not prolonged and did not limit measurements. We have also selected a group of infants aged under 6 months with proved respiratory syncytial viral infection and no previous wheezing or other illness to avoid confounding by case mix. There is considerable confusion about the diagnosis of asthma in this age group and its association with bronchiolitis.

In this study we have demonstrated that infants have significant desaturation when given salbutamol first or after saline nebulisation. Saline nebulisation also caused desaturation; however, the fall in Sao2 was greater and took longer to recover with salbutamol than with saline. The bronchodilator effect after salbutamol inhalation starts at 5–10 minutes and can last up to two to four hours.25 The desaturation noted occurred at the time of maximal action of salbutamol and was consistent whether salbutamol was given first or second. Desaturation was also seen with saline nebulisation, but the effect was smaller, and was more transient than for salbutamol. We assume that the desaturation with saline was related to disturbance of the baby. The mechanism of action of the salbutamol is unclear, but may be due to airway narrowing, vascular dilation leading to shunting, or both. The time course is different to that usually seen in adults with presumed shunting after salbutamol and we would suggest that the salbutamol aerosol also appears to impair ventilation in these infants by an irritant or osmotic effect of the aerosolised nebulising solution.20

Although the median fall in Sao2 was small, there were some infants who demonstrated a drop of 10% or more. These infants had mild disease at the time studied and this effect in an infant with severe disease could be significantly detrimental. Some previous studies have noted hypoxia2 and deterioration in lung function14 21 after bronchodilators in wheezy infants.

Nebulisations do not benefit infants with bronchiolitis who are already distressed. Salbutamol aggravates this process and cannot be recommended. In the event of an uncertain clinical diagnosis when assessment of a response to salbutamol is thought indicated, monitoring with pulse oximetry should be used.

Birth weight and the health of nations

Professor Eva Alberman in her presidential address to the section of epidemiology and public health of the Royal Society of Medicine (Journal of the Royal Society of Medicine 1991;84:257–60) pointed to the value of birthweight statistics as a measure of the health status of a population.

Birth weight is the most powerful predictor of infant survival affecting both neonatal and postneonatal components of infant mortality. Usually the lowest infant mortality is found in babies whose birth weights are about 500 to 1000 g above the mode, although there is a slight increase in mortality at very high birth weights. It is suggested that the disparity between optimal and modal birth weight may be due to the birthweight curve being displaced to the left by the presence at the lower end of the distribution of babies with a pathological cause for their low weight but it is difficult to isolate 'normal' babies to define a pure 'normal' distribution.

Clearly there are biological factors which affect both birth weight and mortality. Girls tend to have a slightly lower birthweight and they have a lower infant mortality for all birth weights. Ethnic differences in birth weight and mortality are probably partly genetic but largely environmental. In the United States the modal birth weight for black babies is about 400 g less than for white. Below a birth weight of about 2000 g infant mortality is less in blacks presumably because small black babies are more 'normal' or more mature than small white babies. At birth weights above 3000 g infant mortality in blacks exceeds that in whites. The findings are similar in relation to maternal smoking: at low birth weights the babies of smoking mothers have a slightly lower mortality than those of non-smokers but babies of smoking mothers who weigh over 3000 g at birth have a higher first year mortality than those of the same birth weight whose mothers do not smoke.

In England and Wales the mean birth weight up to 1986 had changed little over the last 30 years being 3315 g in 1958, 3302 g in 1970, and 3318 g in 1986 but the percentage of babies weighing 3500 g or more at birth rose from 35.9% in 1983 to 38.6% in 1989. Since 1986 there appears to have been some increase in mean birth weight which has been most marked in the less privileged social classes.

A further decrease in maternal smoking and improved maternal health and nutrition among disadvantaged groups would probably lead to higher birth weights and lower infant mortality.