Hypoxaemia in wheezy infants after bronchodilator treatment

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SUMMARY The response of the bronchi to nebulised salbutamol was measured in five recurrently wheezy infants. Changes in oxygenation (measured by pulse oximeter and transcutaneous PO₂ electrodes) and carbon dioxide (measured by transcutaneous PCO₂ electrode) were recorded at the same time. Neither nebulised saline nor salbutamol caused any changes in the measurements of airway function. A significant drop in mean oxygen saturation of 2% and of transcutaneous oxygen tension of 1.3 kPa occurred after nebulised salbutamol. No significant change occurred in measurements of transcutaneous carbon dioxide tension, nor was there any significant change in any of these measurements after 2.5 ml of nebulised saline had been given as a control. These results suggest that nebulised salbutamol may cause significant hypoxaemia, in wheezy infants probably by inducing ventilation/perfusion disturbance.

Nebulised selective β_2 -adrenoceptor agonists are still used in the treatment of wheezing in infants in spite of the evidence that they may be ineffective.¹⁻³ Recently they have been shown to cause deterioration in peripheral airways function in this age group.^{4,5} Because the techniques used for measuring peripheral airway function in wheezy infants are new,^{6,7} it may be that any deterioration noted was artefactual.

In adults and older asthmatic children transient but significant hypoxaemia after treatment with selective β_2 -adrenoceptor agonists has been reported despite improvement in airway patency.⁸⁻¹⁰ This may be the result of a disturbance in ventilation/perfusion balance brought about by pulmonary vasodilatation. If a similar imbalance occurs in the infant lung, without bronchodilation severe hypoxaemia could result.

We assessed the changes in airway function and blood gas measurements after giving nebulised salbutamol to wheezy infants and compared them with a group given nebulised physiological saline.

Patients and methods

Five recurrently wheezy infants (mean age 10.4 months, range 6–15) were studied. They were sufficiently disturbed by wheeze to justify assessment with a view to nebuliser treatment at home.

All were wheezy at the time of testing. The reproducibility of the response to salbutamol was assessed two weeks later in four of the infants. The fifth infant did not have a repeat study because he developed severe bronchoconstriction after the initial treatment with salbutamol.

Sedation with chloral hydrate (100 mg/kg orally) was given 30 minutes before each test. No infant had received any bronchodilator within 24 hours of the test. Ethical committee approval and parental consent were obtained for all studies.

PROCEDURE FOR SALBUTAMOL CHALLENGE

When asleep the infant was placed in a whole body plethysmograph, and baseline measurements of thoracic gas volume and inspiratory airway resistance were made.¹¹ From these, their multiple specific airway resistance was calculated. Partial expiratory flow volume curves were then calculated by suddenly inflating a snugly fitting thoraco-abdominal jacket at the end of a tidal inspiration, thus causing forced expiration.^{6,7} From the flow signal measured through the face mask by the screen pneumotachograph and its integral (volume), a partial expiratory flow volume curve was constructed, and the maximum flow at a lung volume corresponding to functional residual capacity was computed. Six to eight of these manoeuvres were carried out to obtain a mean baseline value for the

maximum flow at functional residual capacity ($\dot{V}_{\max}\text{FRC}$). Reference values for airway resistance and $\dot{V}_{\max}\text{FRC}$ were obtained from previously reported data.^{12 13}

The face mask was removed and 2.5 ml physiological saline at room temperature was given through a Turret nebuliser (Medic Aid) driven by compressed air at 6 l/minute; nebuliser output was directed over the nose and mouth of the sleeping infant, and the nebulisation time was about five minutes. A further set of partial expiratory flow volume curves was then obtained after replacing the face mask and waiting for the baby to settle for five minutes.

After a 20 minute interval 2.5 mg of preservative free salbutamol sulphate in 2.5 ml physiological saline (one Ventolin Nebule) was given by jet nebuliser as described above and further sets of flow volume curves obtained 20 minutes later.

RECORDINGS

Transcutaneous PO_2 (PtcO_2) was monitored using a transcutaneous electrode (Kontron Cutan 820) heated to 44°C and placed on the lower leg after calibration in air. Transcutaneous PCO_2 (PtcCO_2) was monitored using a transcutaneous electrode (Radiometer TCM 20) heated to 43°C and placed on the lower leg after calibration in 10% carbon dioxide. Readings of PtcO_2 and PtcCO_2 were taken

after a stabilisation period of 15 to 20 minutes. A pulse oximeter (Ohmeda Biox 3700) was used to measure arterial oxygen saturation (SaO_2) and heart rate. Data were recorded only when the pulse signal was satisfactory.

Values of SaO_2 , PtcO_2 , PtcCO_2 and heart rate were recorded in the five minutes before and throughout the challenge procedures, and for 20 minutes after the saline and salbutamol had been given. For statistical purposes, comparisons were made between the mean values during the five minute interval before nebulisation and those measured during 0–5 and 15–20 minutes after nebulisation. The paired *t* test was used to test the significance of differences in results after treatment with salbutamol and with saline.

Results

The results for the two study days were similar, with no significant differences between days. Where two sets of data were collected, mean values were used giving one set of results for each of the five patients.

Baseline measurements of lung function indicated that there was definite airway obstruction; the mean (SD) value of specific airway resistance was 249 (106)% of the reference value¹² and the $\dot{V}_{\max}\text{FRC}$ was 24 (8.4)% of the reference value.¹³ Baseline values of PtcO_2 and PtcCO_2 before giving the saline (table) reflect the errors inherent in methods of

Figure Changes in peripheral transcutaneous O_2 before and after nebulised saline and salbutamol. Each point represents mean value over each five minute interval for four infants studied on two occasions each (closed symbols) and one infant studied only once (open symbols).

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Table Mean (SD) values of $\dot{V}_{\text{maxFRC}}$, heart rate, oxygen saturation, transcutaneous PO_2 , and transcutaneous PCO_2 in the five minute intervals before and after nebulised saline and salbutamol

	Nebulised saline				Nebulised salbutamol			
	Before Mean	(SD)	After Mean	(SD)	Before Mean	(SD)	After Mean	(SD)
$\dot{V}_{\text{maxFRC}}$ (ml/sec)	24	(8.4)	25	(6.5)	26	(6.5)	25	(11.1)
Heart rate	133	(15)	132	(14)	135	(17)	151	(14)*
Oxygen saturation (%)	86	(5.6)	86	(5.4)	87	(6.7)	85	(7.0)*
Transcutaneous O_2 (kPa)	7.8	(1.1)	7.7	(1.2)	8.5	(1.5)	7.2	(1.6)†
Transcutaneous CO_2 (kPa)	58	(4.1)	57	(4.1)	56	(3.4)	55	(3.9)

Before and after salbutamol: * $p < 0.01$ † $p < 0.001$.

transcutaneous measurement. The mean value of SaO_2 was significantly lower than normal in these supine, sedated, wheezy infants.

Significant falls in both PtcO_2 ($p < 0.001$; figure) and SaO_2 ($p < 0.01$) occurred within five minutes of giving of nebulised salbutamol, but not after saline (table). The lowest values of PtcO_2 (6.6 kPa) and SaO_2 (84%) occurred at a mean time of 11 minutes after the end of nebulisation. Twenty minutes after the end of nebulisation the mean value for PtcO_2 of 7.1 kPa was still significantly lower than the mean value of 8.5 kPa before salbutamol ($p < 0.01$), although the SaO_2 had returned to the baseline value.

There were small changes in PtcCO_2 measurements. The small decline after salbutamol had been given was not significant (table). Mean heart rate increased significantly after salbutamol was started, the increase persisting for at least 20 minutes after nebulisation had stopped. There was no significant change in heart rate with nebulised saline.

Discussion

We found a significant deterioration in oxygenation in wheezy infants after they had been given salbutamol. These changes were similar to those reported in older asthmatic children and adults.⁸⁻¹⁰ There was a small decline in PtcCO_2 in conjunction with the hypoxaemia. In adults these changes probably reflect an increase in ventilation/perfusion disturbance secondary to pulmonary vasodilatation. There were certainly cardiovascular effects in our infants, shown by tachycardia. Ventilation/perfusion disturbances may be more likely to occur in infants, because babies do not have any of the ameliorating effects of bronchodilatation in response to salbutamol, in spite of the fact that they do have functional airway β -adrenoceptors.¹⁴ Airway obstruction may actually increase after bronchodilation, contributing to hypoxaemia.⁴

Jet nebulisation causes a gradual increase in the osmolality of the nebulisate. This is more likely to occur with long nebulisation times and small starting volumes,¹⁵ and occurs with both the nebulised saline and with salbutamol.^{15 16} This increase in osmolality could explain the adverse effects on airway function in wheezy infants, although these effects seem to be short lived.¹⁷

In contrast both the hypoxic effects of salbutamol and the decline in forced expiratory flow rates were still present 20 minutes after nebulisation, suggesting a persistent pharmacological effect.⁴

The validity of our results may be questioned because these infants were studied while asleep under sedation with chloral hydrate. Although oxygen consumption and production of carbon dioxide have been shown to be slightly higher in infants under sedation with chloral hydrate, this type of sedation produces steady oxygen consumption, endogenous carbon dioxide production, and end tidal PCO_2 , and does not affect carbon dioxide chemoreceptor responsiveness, thus providing stable baseline readings from which to calculate changes in oxygen and carbon dioxide concentrations.¹⁸ Face mask application causes changes in respiratory patterns in infancy.¹⁹ All recordings of SaO_2 , PtcO_2 , and PtcCO_2 were taken after removal of the face mask, allowing for a period of stabilisation.

Transcutaneous measurements provide indirect values for PaO_2 and PaCO_2 , but these values do bear a close and proportional correlation with the true values.²⁰⁻²³ Changes in transcutaneous values should therefore indicate arterial changes as long as the coefficient of proportionality remains unchanged. We cannot be sure that nebulised salbutamol did not change cutaneous blood flow, but the relative stability of PCO_2 readings argues against this. In addition, the parallel decline in SaO_2 and PtcO_2 reinforces the validity of the transcutaneous measurements.

This study has important clinical implications. As well as showing a paradoxical effect on airway function in wheezy infants,⁴ we have shown that nebulised bronchodilators may have an adverse effect on arterial oxygenation. The effect persisted for at least 20 minutes. It may be that in the presence of more severe airway obstruction and hypoxaemia a more severe adverse reaction to nebulised bronchodilator could occur: this would require urgent treatment with oxygen.

We are grateful to Mr N Levy and Mr J Messeguer for technical help. The work was supported by the Asthma Research Council, Allen & Hanburys Ltd, and Hammersmith and Queen Charlotte's Special Health Authority.

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Received 26 May 1987