ORIGINAL ARTICLES

Hypoxaemia after nebulised salbutamol in wheezy infants: the importance of aerosol acidity

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Abstract

The effect of nebulised iso-osmolar, preservative free, but acidic salbutamol solution was studied in 34 acutely wheezing infants aged 1-17 months. Transcutaneous oxygen pressure (TcPo₂) and oxygen saturation (So₂) fell significantly during the first five minutes after nebulisation with further deterioration at 15-20 minutes. Ten of these infants were followed up for another two hours and showed slight improvement. Even after the second hour TcPo₂ had not reached baseline values. Three months later the response to salbutamol and a placebo of equal acidity (pH 3.9) was studied in 11 infants from the same group, now free of symptoms. Lung function tests were included and showed no significant changes in specific conductance and volume corrected maximum expiratory flows ($\dot{V}_{max}$ at functional residual capacity/thoracic gas volume). However, hypoxaemia occurred after the acidic placebo with a significant drop of TcPo₂ (mean 0.9 kPa); So₂ decreased similarly but this did not reach significance. After salbutamol there was a further significant deterioration of mean TcPo₂ (1.4 kPa) and of So₂. These results show that beside a possible pharmacological effect of salbutamol the acidity of the aerosol also induces hypoxaemia in infants.

Nebulised salbutamol has been shown to cause hypoxaemia in acutely wheezy infants.¹ Similarly, several lung function parameters of wheezy infants were found to deteriorate after nebulisation of salbutamol,²⁻⁴ but their relation to hypoxaemia has not been proved. The mechanisms of hypoxaemia after inhalation of salbutamol are still unclear. An increase of ventilation-perfusion mismatch could be caused by raised pulmonary perfusion⁵ as well as reduced airway smooth muscle tone leading to higher airway compression during forced expiration.²⁻³ Also the physical properties of the aerosol including acidity and osmolarity⁴ or the content of preservative⁶ may be responsible for the observed negative effects. Furthermore hypoxaemia could be explained by a rise in oxygen consumption, which may be induced by salbutamol⁷ or just by the sedation (chloral hydrate),⁸ which is often used to perform the lung function tests.

The clinically important observation of hypoxaemia after nebulisation of salbutamol has so far been made in only five wheezy infants, who all were sedated with chloral hydrate.¹ The observation period was no longer than 20

minutes and oxygen pressure did not return to baseline during that time period. The placebo used was physiological saline; the salbutamol solution however was acidic.^{1,9}

We therefore performed two test series to obtain further information. In both tests transcutaneous oxygen pressure (TcPo₂) and saturation (So₂) were measured after nebulisation of a preservative free and iso-osmolar salbutamol solution. In the first test acutely wheezing infants were studied without sedation over a period of 2.5 hours. From these, some infants could be re-examined when free of symptoms with additional lung function tests before and after salbutamol and placebo of equal acidity.

Patients and methods

For the first test, 34 acutely wheezy infants aged 1-17 months (mean age 6.6 months) were studied shortly after admission to hospital. Readings of TcPo₂ (Kontron Cutan 820) were taken after calibration in air by placing the heated electrode (44°C) on the upper thorax of the infants and allowing a stabilisation period of 15-20 minutes. Heart rate and So₂ (Dräger Nellcor 100) were recorded simultaneously, and special care was taken to discard artefacts. All the readings were only taken when the infants were asleep or lying quietly without body movements.

The patients were not sedated and had not received any bronchodilator during the previous eight hours. An iso-osmolar solution containing 2.5 mg of preservative free salbutamol (2.5 ml Salbutamol 5 Riker Infusionskonzentrat, 290 mosm/kg, pH 3.9) were given by a Turret nebuliser (Medic Aid) driven by compressed air at 6 l/minute for about five minutes. TcPo₂ and So₂ were observed continuously, values were collected at minute intervals, and the mean values for the five minutes before and after nebulisation were analysed as well as the mean values from the 15th to 20th minute.

After measurements had been obtained from 15 patients, we decided to extend the observation period and 10 patients could be follow up to 2.5 hours. The means from 60-80 minutes and 120-140 minutes after nebulisation were recorded.

Informed consent was obtained from parents of 11/34 infants to participate in a second test about three months later when the infants were without clinical symptoms and free of infection. Their mean age then was 9.5 months (range 6-14 months). They received 80-100 mg/kg chloral hydrate orally. When asleep, baseline values for airway resistance and thoracic gas

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volume (TGV) were measured in a volume constant baby body plethysmograph (Fenyves and Gut) under body temperature, pressure, and saturation (BTPS) conditions. Maximum flow at functional residual capacity (FRC) (Vmax FRC) was obtained by the chest compression technique described elsewhere.^{10 11} TcPO₂, SO₂ and heart rate were recorded as described above. An aliquot of 2.5 ml of acidic placebo (physiological saline, titrated to pH 3.9 with hydrochloric acid, osmolality 280 mosm/kg) was nebulised with the same Turret nebuliser and flow rate for about five minutes. Fifteen to 20 minutes later the infants received the same dose of salbutamol as in the first test. After both nebulisations measurements of TcPO₂, SO₂ and heart rate were averaged for the first five minutes after nebulisation and lung function tests were repeated.

The Wilcoxon matched paired test for non-parametric data was used to describe significant differences (*p*<0.05). These were similar to results obtained using equivalent *t* tests, therefore values are expressed as mean and SD.

Results

FIRST TEST: ACUTELY WHEEZY INFANTS

Thirty of 34 infants remained undisturbed

Table 1 Mean (SD) values of oxygen saturation (SO₂), transcutaneous oxygen pressure (TcPO₂), and heart rate before and up to 20 minutes after salbutamol (n=30)

	Baseline	0-5 Minutes	15-20 Minutes
SO ₂ (%)	95 (3.8)	93 (4.6)*	93 (4.5)*
TcPO ₂ (kPa)	8.2 (1.8)	7.5 (1.9)*	7.2 (1.9)*†
Heart rate (1/min)	131 (18)	135 (18)*	139 (17)*†

*Significantly different (*p*<0.05) to baseline value; †significantly different (*p*<0.05) to preceding value.

Figure 1 Individual changes in transcutaneous oxygen pressure (TcPO₂) 20 minutes after salbutamol (n=30). A fall was observed in 28 and an increase in two infants.

throughout the test, but four infants fell asleep or woke up so that comparable measurements could not be obtained.

Baseline readings for TcPO₂ and SO₂ are listed in table 1. After salbutamol a significant fall occurred for TcPO₂ and SO₂ within the first five minutes (*p*<0.001). Further deterioration was observed after 15-20 minutes. Compared with baseline values, the mean TcPO₂ had decreased from 8.2 kPa to 7.2 kPa and SO₂ from 95% to 93%. Individual changes are shown in fig 1.

The long term follow up in 10 patients showed improvement after one and two hours, TcPO₂ still remaining significantly below the baseline values (7.1 kPa, *p*<0.006 and 7.4 kPa, *p*<0.047) (table 2, fig 2). SO₂ had normalised after the second hour except in five patients with values of more than 1% below the baseline value. Mean heart rate rose significantly after salbutamol from 131/minute to a maximum of 139/minute 20 minutes after nebulisation. After one hour heart rate was still raised (*p*<0.007).

SECOND TEST: INFANTS FREE OF SYMPTOMS

Three of 11 infants woke up after the measurements taken after the placebo. Only complete data sets were compared: for TcPO₂ and SO₂ this was obtained in eight infants; for airway mechanics in six infants only.

Baseline readings for TcPO₂ (10.4 kPa) and SO₂ (98%) had now reached normal range in most patients (table 3). After nebulisation of the acidic placebo, values for TcPO₂ fell significantly to 9.5 kPa (*p*<0.012) within the first five minutes and recovered to 10.0 kPa within the 15th to 20th minute after nebulisation (*p*=0.164, fig 3). However, TcPO₂ was still significantly different from baseline (*p*<0.013). After

Figure 2 Changes in transcutaneous oxygen pressure (TcPO₂) up to 2.5 hours after salbutamol (n=10). The bold line indicates the mean value.

Table 2 Mean (SD) values of oxygen saturation (SO₂), transcutaneous oxygen pressure (TcPO₂), and heart rate before and up to 2.5 hours after salbutamol (n=10)

	Baseline	0-5 Minutes	15-20 Minutes	60-80 Minutes	120-140 Minutes
SO ₂ (%)	93 (2.7)	91 (4.4)*	91 (4.5)*	92 (3.4)*	92 (3.2)
TcPO ₂ (kPa)	8.1 (2.4)	7.1 (2.4)*	6.9 (2.4)*	7.1 (2.4)*	7.4 (2.7)*
Heart rate (1/min)	127 (12)	132 (14)*	134 (15)*†	134 (13)*	129 (16)†

*Significantly different (*p*<0.05) to baseline value; †significantly different (*p*<0.05) to preceding value.

Table 3 Mean (SD) values of oxygen saturation (SO₂), transcutaneous oxygen pressure (TcPO₂), heart rate, and lung function (% predicted) at baseline, after acidic placebo, and after salbutamol

	No of patients	Baseline	After placebo: early	After placebo: late	After salbutamol
SO ₂ (%)	8	98 (1.1)	97 (2.2)	98 (1.3)	96 (2.0)*†
TcPO ₂ (kPa)	8	10.4 (1.3)	9.5 (1.9)*	10.0 (1.4)*	8.6 (1.8)*†‡
Heart rate (1/min)	8	122 (10.9)	125 (8.2)	122 (10.8)	141 (10.8)*†‡
Vmax FRC (%)	6	48 (18)	42 (16)	—	50 (22)
Airway resistance (%)	6	95 (28)	114 (23)	—	119 (27)
TGV (%)	6	147 (20)	130 (18)*	—	132 (21)
Specific conductance (1/second/kPa)	6	0.16 (0.05)	0.14 (0.05)	—	0.13 (0.04)
Vmax FRC/TGV (1/second)	6	0.41 (0.18)	0.40 (0.18)	—	0.47 (0.22)

*Significantly different (p<0.05) to baseline value; †significantly different (p<0.05) to after placebo, late; ‡significantly different (p<0.05) to after placebo, early.
FRC, functional residual capacity; TGV, thoracic gas volume.

Figure 3 Changes in transcutaneous oxygen pressure (TcPO₂) after acidic placebo (n=11) and after salbutamol (n=8). The bold line indicates the mean value.

salbutamol TcPO₂ decreased even further to 8.6 kPa, significantly different from baseline values (p<0.012) and from both readings after placebo (p<0.018 and p<0.012). Smaller changes could be observed with SO₂ (table 3), the only significant difference occurring between before and after salbutamol (p<0.012).

Baseline lung function expressed as percentage of predicted values^{10 12} were normal for airway resistance (95%), raised for TGV (147%) and decreased for Vmax FRC (48%), indicating a persisting small airway obstruction; therefore specific conductance (0.16/second/kPa) and VmaxFRC/TGV (0.41/second) were diminished (table 3).

After the acidic placebo airway resistance increased to 114% predicted (p=0.141), TGV decreased to 130% predicted (p<0.028), and specific conductance remained little changed (0.14/second/kPa, p=0.465). VmaxFRC decreased slightly to 42% (p<0.044), but Vmax FRC/TGV remained unchanged (0.40/second, p=0.465).

Lung function after salbutamol was not significantly different to baseline and after placebo values.

Discussion

In the present study on 34 infants we have confirmed the clinically important observation of Prendiville *et al*, that is, that hypoxaemia occurs after nebulisation of salbutamol in wheezy infants.¹ This is not only a transient effect, as

we have shown persistence of low values for oxygen pressure up to two hours thereafter. Our patients were not sedated. We also used an iso-osmolar solution, and although an increase in osmolarity during nebulisation has been described,⁴ neither bronchoconstriction nor hypoxaemia¹ has been shown after physiological saline. Our solution did not contain preservatives also known to evoke bronchoconstriction.^{6 13}

The salbutamol solution we used, however, was acidic. For the lung function tests we therefore decided to use a placebo of equal acidity, which to our knowledge has not been reported so far. Citric acid has been nebulised to dogs inducing airway obstruction with two mechanisms being suggested by the authors: reflex bronchoconstriction after a nebulisation period of two minutes and a mediator induced bronchoconstriction after nebulisation for five minutes.¹⁴ Swallowing an acidic solution may also lead to airway obstruction,¹⁵ and as in nebulisation a considerable amount of aerosol is swallowed this too has to be taken into account. There are also some reports that in adults bronchoconstriction may occur after inhalation of various acidic aerosols.¹⁶⁻¹⁸

In infants O'Callaghan *et al* have observed deterioration of specific conductance after nebulisation of a preservative free, iso-osmolar but acidic (pH 3.6) solution of ipratropium bromide.¹⁹ This effect was short lived—lasting for about 10–15 minutes. Similarly, deterioration of airway resistance, specific conductance,⁴ and Vmax FRC³ has been reported after an acidic salbutamol solution. In the present study we could not find significant deterioration in airway resistance, specific conductance or Vmax FRC/TGV after placebo or salbutamol. A possible explanation may be that we measured lung function between seven and 13 minutes after nebulisation to avoid disturbance of oxygen measurements, so we might have missed an initial reaction of airway mechanics. However, we did notice a significant drop of TcPO₂ after nebulisation of the acidic placebo which did not fully recover by 20 minutes.

From these results the question arises whether hypoxaemia after salbutamol could be a preventable side effect not related to the drug itself but to acidity. We did not nebulise a neutral salbutamol solution and therefore cannot answer this question definitively. Although severity and duration of hypoxaemia were more pronounced after salbutamol than after placebo,

this could be explained by an additive effect of nebulising an acidic aerosol twice. However, in our first test the fall in $TcPO_2$ related well to the rise of heart rate which persisted for more than one hour after salbutamol. This could indicate that hypoxaemia was due to a systemic effect of salbutamol. Inhaled as well as intravenously administered salbutamol may cause ventilation-perfusion mismatch, which could result from an increase in pulmonary perfusion into relatively less ventilated areas.⁵⁻²⁰ Furthermore, there has been evidence for increased oxygen consumption after salbutamol in monkeys⁷ and adult asthmatics,⁵ which offers another explanation for the observed hypoxaemia.

As we did not notice any significant effects of salbutamol on lung function, we cannot confirm the findings of other authors that in infants reduction in smooth muscle tone might render the airways less capable of supporting high flow rates during forced expiration.²⁻²¹

In conclusion we believe that salbutamol does have a pharmacological effect causing hypoxaemia. What we could prove is that acidity itself induces hypoxaemia and may therefore enhance the negative effects of salbutamol. We therefore recommend that nebuliser solutions should be neutralised as far as possible and more information concerning the different properties of the aerosols be made available.

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- 1 Prendiville A, Rose A, Maxwell DL, Silverman M. Hypoxaemia in wheezy infants after bronchodilator treatment. *Arch Dis Child* 1987;62:997-1000.
- 2 Hughes DM, LeSouef PN, Landau LI. Effect of salbutamol on respiratory mechanics in bronchiolitis. *Pediatr Res* 1987;22:83-6.

- 3 Prendiville A, Green S, Silverman M. Paradoxical response to nebulised salbutamol in wheezy infants, assessed by partial expiratory flow-volume curves. *Thorax* 1987;42:86-91.
- 4 O'Callaghan C, Milner AD, Swarbrick A. Paradoxical deterioration in lung function after nebulised salbutamol in wheezy infants. *Lancet* 1986;ii:1424-5.
- 5 Ballester E, Reyes A, Roca J, Guitart R, Wagner PD, Rodriguez-Roisin R. Ventilation-perfusion mismatching in acute severe asthma: effects of salbutamol and 100% oxygen. *Thorax* 1989;44:258-67.
- 6 Beasley CR, Rafferty P, Holgate ST. Bronchoconstrictor properties of preservatives in ipratropium bromide (Atrovent) nebuliser solution. *BMJ* 1987;294:1197-8.
- 7 Newth C. Pulmonary and metabolic responses to inhaled salbutamol (albuterol) in monkeys (*Macaca mulatta*). *Am Rev Respir Dis* 1989;139:A564.
- 8 Bouhuys A, van de Woestijne KP. Mechanical consequences of airway smooth muscle relaxation. *J Appl Physiol* 1971;30:670-6.
- 9 Prendiville A, Silverman M. Paradoxical response to nebulised salbutamol in wheezy infants. *Thorax* 1987;42:702-3.
- 10 Masters IB, Seidenberg J, Hudson I, Phelan PD, Olinsky A. Longitudinal studies of lung mechanics in normal infants. *Pediatr Pulmonol* 1987;3:3-7.
- 11 Seidenberg J, Masters IB, Hudson I, Olinsky A, Phelan PD. Disturbance in respiratory mechanics in infants with bronchiolitis. *Thorax* 1989;44:660-7.
- 12 Radford M. Measurements of airway resistance and thoracic gas volume in infancy. *Arch Dis Child* 1974;49:611-5.
- 13 Zhang YG, Wright WJ, Tam WK, Nguyen-Dang TH, Salome CM, Woolcock AJ. Effect of inhaled preservatives on asthmatic subjects. *Am Rev Respir Dis* 1990;141:1405-8.
- 14 Hirshman CA, Peters J, Downes H, et al. Citric acid airway constriction in dogs with hyperreactive airways. *J Appl Physiol* 1983;54:1101-7.
- 15 Wilson NM, Chudry N, Silverman M. Role of the oesophagus in asthma induced by the ingestion of ice and acid. *Thorax* 1987;42:506-10.
- 16 Balmes JR, Fine JM, Christian D, Gordon T, Sheppard D. Acidity potentiates bronchoconstriction induced by hypo-osmolar aerosols. *Am Rev Respir Dis* 1988;138:35-9.
- 17 Utell MJ, Morrow PE, Speers DM, Darling J, Hyde RW. Airway responses to sulfate and sulfuric acid aerosols in asthmatics. *Am Rev Respir Dis* 1983;128:444-50.
- 18 Fine JM, Gordon T, Thompson JE, Sheppard D. The role of titratable acidity in acid aerosol-induced bronchoconstriction. *Am Rev Respir Dis* 1987;135:826-30.
- 19 O'Callaghan C, Milner AD, Swarbrick A. Paradoxical bronchoconstriction in wheezing infants after nebulised preservative free iso-osmolar ipratropium bromide. *BMJ* 1989;299:1433-4.
- 20 Harris L. Comparison of the effect on blood gases, ventilation, and perfusion of isoproterenol-phenylephrine and salbutamol aerosols in chronic bronchitis with asthma. *J Allergy Clin Immunol* 1971;49:63-71.
- 21 Prendiville A, Green S, Silverman M. Airway responsiveness in wheezy infants: evidence for functional β adrenergic receptors. *Thorax* 1987;42:100-4.