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

J Seidenberg, Y Mir, H von der Hardt

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 (Vmax 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. Similarly, several lung function parameters of wheezy infants were found to deteriorate after nebulisation of salbutamol 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 perfusion as well as reduced airway smooth muscle tone leading to higher airway compression during forced expiration. Also the physical properties of the aerosol including acidity and osmolality or the content of preservative may be responsible for the observed negative effects. Furthermore hypoxaemia could be explained by a rise in oxygen consumption, which may be induced by salbutamol or just by the sedimentation (chloral hydrate), 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. 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.

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 followed 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
test described elsewhere. 10

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, osmolarity 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 pairs test for non-
parametric data was used to describe significant
differences (p<0.05). These were similar to
results obtained using equivalent t tests, there-
fore values are expressed as mean and SD.

Results

FIRST TEST: ACUTELY WHEEZY INFANTS

Thirty of 34 infants remained undisturbed
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 show-
red 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 measure-
ments taken after the placebo. Only complete
data sets were compared: for TcPO2 and So2 this
was obtained in eight infants; for airway mecha-

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)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>0-5 Minutes</th>
<th>15-20 Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>So2 (%)</td>
<td>95 (3.8)</td>
<td>93 (4.6)*</td>
<td>93 (4.5)*</td>
</tr>
<tr>
<td>TcPO2 (kPa)</td>
<td>8.2 (1.8)</td>
<td>7.5 (1.9)*</td>
<td>7.2 (1.9)*</td>
</tr>
<tr>
<td>Heart rate (1/min)</td>
<td>131 (18)</td>
<td>135 (18)*</td>
<td>139 (17)*</td>
</tr>
</tbody>
</table>

*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.

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)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>0-5 Minutes</th>
<th>15-20 Minutes</th>
<th>60-80 Minutes</th>
<th>120-140 Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>So2 (%)</td>
<td>93 (2.7)</td>
<td>91 (4.4)*</td>
<td>91 (4.5)*</td>
<td>92 (3.4)*</td>
<td>92 (3.2)</td>
</tr>
<tr>
<td>TcPO2 (kPa)</td>
<td>8.1 (2.4)</td>
<td>7.1 (2.4)*</td>
<td>6.9 (2.4)*</td>
<td>7.1 (2.4)*</td>
<td>7.4 (2.7)*</td>
</tr>
<tr>
<td>Heart rate (1/min)</td>
<td>127 (12)</td>
<td>132 (14)*</td>
<td>134 (15)*†</td>
<td>134 (13)*</td>
<td>129 (16)†</td>
</tr>
</tbody>
</table>

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

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 3 Mean (SD) values of oxygen saturation (\(S_0_2\)), transcutaneous oxygen pressure (\(TcPo_2\)), heart rate, and lung function (% predicted) at baseline, after acidic placebo, and after salbutamol

<table>
<thead>
<tr>
<th></th>
<th>No of patients</th>
<th>Baseline</th>
<th>After placebo: early</th>
<th>After placebo: late</th>
<th>After salbutamol</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S_0_2) (%)</td>
<td>8</td>
<td>98 (1-1)</td>
<td>97 (2-2)</td>
<td>98 (1-3)</td>
<td>96 (2-0)*</td>
</tr>
<tr>
<td>(TcPo_2) (kPa)</td>
<td>8</td>
<td>10-4 (1-3)</td>
<td>9-5 (1-9)*</td>
<td>10-0 (1-4)*</td>
<td>8-6 (1-8)*††</td>
</tr>
<tr>
<td>Heart rate (1/min)</td>
<td>8</td>
<td>122 (10-9)</td>
<td>125 (8-2)</td>
<td>122 (10-8)</td>
<td>141 (10-7)*‡‡</td>
</tr>
<tr>
<td>Vmax FRC (%)</td>
<td>6</td>
<td>48 (18)</td>
<td>42 (16)</td>
<td>—</td>
<td>50 (22)</td>
</tr>
<tr>
<td>Airway resistance</td>
<td>6</td>
<td>95 (28)</td>
<td>114 (23)</td>
<td>—</td>
<td>119 (27)</td>
</tr>
<tr>
<td>TGV (%)</td>
<td>6</td>
<td>147 (20)</td>
<td>130 (18)*</td>
<td>—</td>
<td>132 (23)</td>
</tr>
<tr>
<td>Specific conductance (1/second/kPa)</td>
<td>6</td>
<td>0-16 (0-05)</td>
<td>0-14 (0-05)</td>
<td>—</td>
<td>0-13 (0-04)</td>
</tr>
<tr>
<td>Vmax FRC/TGV (1/second)</td>
<td>6</td>
<td>0-41 (0-18)</td>
<td>0-40 (0-18)</td>
<td>—</td>
<td>0-47 (0-22)</td>
</tr>
</tbody>
</table>

*Significantly different (p<0-05) to baseline values; †significantly different (p<0-05) to acidic placebo, early; ‡significantly different (p<0-05) to acidic placebo, late; ‡‡significantly different (p<0-05) to acidic placebo, late.

FRC, functional residual capacity; TGV, thoracic gas volume.

Salbutamol \(TcPo_2\) 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 \(S_0_2\) (table 3), the only significant difference occurring between before and after salbutamol (p<0-012).

Baseline lung function expressed as percentage of predicted values 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 \(V_{max}FRCTGV\) (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. 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, neither bronchoconstriction nor hypoxaemia has been shown after physiological saline. Our solution did not contain preservatives also known to evoke bronchoconstriction.

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. Swallowing an acidic solution may also lead to airway obstruction, 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.

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. This effect was short lived—lasting for about 10–15 minutes. Similarly, deterioration of airway resistance, specific conductance, and Vmax FRC 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 \(TcPo_2\) 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 TcPo2 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.20 Furthermore, there has been evidence for increased oxygen consump-
tion after salbutamol in monkeys6 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.20

In conclusion we believe that salbutamol does have a pharmacological effect causing hypox-
aemia. 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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