Nebulised racemic adrenaline in the treatment of acute bronchiolitis in infants and toddlers

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Abstract
The effect of inhaled nebulised racemic adrenaline upon symptoms of acute bronchiolitis was investigated in 29 infants and toddlers aged 2-17.5 months by transtracheal oxygen tension (TcPO₂), oxygen saturation, transtracheal carbon dioxide tension (TcPCO₂), and clinical evaluation in a double blind placebo controlled study.

Clinical score and TcPO₂ improved significantly at 30, 45, and 60 minutes after inhalation of racemic adrenaline, with an increase in TcPO₂ ≥0.5 kPa in 72% of the children <1 year of age. No significant improvement was observed after inhalation of placebo.

No significant changes in heart rate or TcPCO₂ were observed from before to after inhalation, but a small increase in mean systolic blood pressure was observed immediately and 45 minutes after racemic adrenaline inhalation.

This study demonstrates that treatment with nebulised racemic adrenaline improved oxygenation and clinical signs in hospitalised children aged less than 18 months with bronchiolitis.

The efficacy of the commonly used bronchodilators in infants and toddlers with acute bronchiolitis is not well established.1-3 In this age group, inflammation and oedema of the airways may contribute substantially to the obstruction in the lower airways. Thus, treatment with a combined α and β agonist should theoretically be beneficial. The rationale for including the α agonist component would be that α receptor stimulation reduces capillary and postcapillary microvascular leakage, mainly by constricting the precapillary bronchial arterioles. This reduces capillary and postcapillary hydrostatic pressure reversing the fluid leakage to resorption, thus reducing bronchial mucosal oedema.4

In a previous study in which inhaled nebulised racemic adrenaline was given openly to young children as treatment for acute bronchiolitis, beneficial effects on transtracheal oxygen tension (TcPO₂) and oxygen saturation (SaO₂) were demonstrated.5 Significant improvement was observed in these children from 2 months of age. As the documentation for a possible effect of nebulised racemic adrenaline in infants and toddlers with acute bronchiolitis is scarce, a double blind placebo controlled study was designed to investigate this further.

Subjects and methods
SUBJECTS
The first 34 eligible children admitted to hospital for acute bronchiolitis were included in the study after informed consent was obtained from one or both parents. They all fulfilled the criteria of age less than 18 months, no atopic eczema, diagnosis of bronchiolitis according to the criteria of Court,6 and a symptom score of 4 or more on a scale from 0 to 10 based on a clinical scoring system as described in table 1. Arousal state (sleeping; awake and calm; and awake and crying) was registered together with the other parameters before inhalation and immediately after, 15, 30, 45, and 60 minutes after inhalation. Changes in arousal state influence blood gas levels.7 As five of the 34 children had a different arousal state before treatment compared with the periods after, these were excluded before the final analysis. Thus, the results of 29 patients were analysed and are reported in this paper.

Infants were randomly selected to the actively treated group or the placebo group at inclusion in the study. Fifteen children received inhaled racemic adrenaline (Vaponefrin, Fisons, 20 mg/ml), and 14 children received an inhalation of placebo. There were no significant differences between the two treatment groups in gender, age, weight, or duration of respiratory tract infection symptoms and duration of wheeze before inclusion in the study, as shown in table 2. In both groups three children had their second, and one their fourth, wheezing episode. In the adrenaline group 4/15 had siblings with asthma, 3/15 parents with asthma, and 6/15 (40%) either parents or siblings with asthma. The corresponding figures for the placebo group were 3/14, 2/14, and 5/14 (36%).

METHODS
Assessments of the parameters described (table 1) were performed before and immediately after inhalation, and every 15 minutes thereafter for the next hour. The study was
Table 2 Characteristics of the subjects in the two treatment groups; results are mean (range) except for gender

<table>
<thead>
<tr>
<th></th>
<th>Racemic adrenaline</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Boys/girls</td>
<td>10/5</td>
<td>9/5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>8-3 (6-9-11.3)</td>
<td>8-6 (4-7-12.0)</td>
</tr>
<tr>
<td>Duration of wheeze (days)*</td>
<td>3-4 (0-5-8-0)</td>
<td>2-6 (0-2-4-0)</td>
</tr>
<tr>
<td>Duration of infection (days)*</td>
<td>4-2 (0-5-11.0)</td>
<td>4-2 (0-6-10.0)</td>
</tr>
</tbody>
</table>

There were no statistically significant differences in characteristics in the two treatment groups. 
*Duration of wheeze and infection are the mean duration of symptoms of bronchopulmonary obstruction and of respiratory infection respectively.

The results are given as mean values with 95% confidence intervals (CI) in parentheses unless otherwise stated. Demographic data are given in table 2. The statistical comparison within each group is made from preinhalation to postinhalation values using Wilcoxon signed rank test for analysis. Differences between groups were analysed by the Mann-Whitney U test. Results were considered statistically significant with p values less than 5%.

Results

The baseline clinical score was 4-5 (95% CI 4-0 to 5-0) and 4-6 (3-9 to 5-4) in the actively treated and placebo group, respectively. The mean baseline values for TcPo2, Sao2, and TcPCO2 are shown in table 3. Despite randomisation, the mean TcPo2 was significantly lower in the actively treated compared with placebo group at the time of inclusion (p<0.05). No other significant differences were found between the two groups at this time.

Significant improvement from before to immediately after inhalation of adrenaline was found for TcPo2 (p<0-01), Sao2, and symptom score (p<0-05) in the adrenaline treated group. In this group, but not in the placebo group, the mean TcPo2 improved significantly from before to 30 (p<0-001), 45 (p<0-01), and 60 (p<0-05) minutes after inhalation, as shown in fig 1. In the group receiving placebo, the TcPo2 improved significantly immediately after inhalation (p<0-01), but not thereafter (fig 1). In 72% of children below 1 year of age receiving adrenaline, the TcPo2 improved >0-5 kPa at 15, 30, 45, and 60 minutes after inhalation.

The improvement of Sao2 for all infants in the adrenaline treated group was significant (p<0-05) immediately after inhalation, but not thereafter (fig 1). No improvement was seen at any time in the group receiving placebo (fig 1). In the most severely affected infants (those with a baseline Sao2 ≤93%), the Sao2 remained significantly (p<0-05) improved throughout the one hour period after inhalation of adrenaline (n=11).

Mean symptom score improved significantly at all intervals after inhalation of adrenaline, but not after inhalation of placebo (fig 1). No significant changes in TcPCO2 were found in either treatment group.

Mean respiratory rate decreased significantly (p<0-05) at 45 minutes after inhalation of adrenaline, but no significant changes were observed in the placebo group (fig 2). Heart rate did not change significantly throughout the study period in either group. However, a significant (p<0-05), although small increase in mean systolic blood pressure was observed in the adrenaline treated group at the immediate postinhalation and the 45 minutes’ reading (fig 2).

Table 3 The baseline (preinhalation) values for TcPo2, Sao2, and TcPCO2 in the two treatment groups; results are mean (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Racemic adrenaline</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>TcPo2 (kPa)</td>
<td>7-0 (5-9 to 8-1)</td>
<td>8-3 (7-7 to 8-9)</td>
</tr>
<tr>
<td>Sao2 (%)</td>
<td>90-8 (87-9 to 93-7)</td>
<td>92-5 (91-3 to 93-7)</td>
</tr>
<tr>
<td>TcPCO2 (kPa)</td>
<td>4-8 (4-5 to 5-2)</td>
<td>4-5 (4-1 to 4-9)</td>
</tr>
</tbody>
</table>

Baseline TcPo2 was significantly lower in the actively treated group than in the placebo group (p<0-05), but Sao2 and TcPCO2 did not differ significantly between the groups.
The present study was to evaluate the effect of adrenaline upon the symptoms and signs of acute bronchiolitis.

Although clinical scoring is based on subjective evaluation it is nevertheless valuable, as possible observer bias was eliminated by the double blind placebo controlled design of the study. Objective criteria such as measurements of transcutaneous blood gases and pulse oximetry, have previously been shown useful in the evaluation of drug effects on acute bronchopulmonary obstruction in infants and children. These techniques are popular as they are non-invasive, require a minimum of cooperation from the child, and do not necessitate sedation. A good correlation between increasing severity of bronchopulmonary obstruction evaluated by a clinical symptom grading system, and a decline in $TcPo_2$, has previously been demonstrated in children aged 5–22 months. As transcutaneous blood gas measurements may be misleading in infants with eczema, children with obvious eczema were not eligible in the current study. Thus, in the present study, an evaluation of possible effects of inhaled racemic adrenaline was based upon both clinical evaluation, objective

Discussion

Little is known about the possible effect of inhaled nebulised racemic adrenaline in infants and toddlers with acute bronchiolitis. The drug and this administration route is widely used in upper respiratory tract obstruction (croup), but is scarcely documented for lower airways obstruction in infants and toddlers.

Virological diagnosis was not an inclusion criterion in the present study. Earlier studies have been done in both hospitals to evaluate the virological agents causing bronchiolitis, demonstrating presence of respiratory syncytial virus in 50–80%.

Figure 1 $TcPo_2$, $SaO_2$ and clinical score (mean with 95% CI) before (baseline), immediately after inhalation (0), and 15, 30, 45, and 60 minutes after inhalation in the groups inhaling racemic adrenaline (n=15) and placebo (n=14). Significant differences from before to after inhalation are shown as: * p<0.05; ** p<0.01. Significant differences between the groups were found for $TcPo_2$ at 30 and 45 minutes, and for $SaO_2$ at 30, 45, and 60 minutes after inhalation (shown as horizontal bars).

At 30 and 45 minutes the $TcPo_2$ (expressed as units kPa change from baseline) was significantly higher in the group receiving adrenaline compared to the placebo group (fig 1). Similar findings were made for $SaO_2$ (expressed as per cent change from baseline) at 15, 30, and 45 minutes (fig 1).

Figure 2 Respiratory rate, heart rate, systolic and diastolic blood pressure (mean with 95% CI) before (baseline), immediately after inhalation (0), and 15, 30, 45, and 60 minutes after inhalation in the groups inhaling racemic adrenaline (n=15) and placebo (n=14). Significant differences from before to after inhalation are shown as: * p<0.05; ** p<0.01.
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measurements of transcutaneous blood gases, and pulse oximetry.

Despite randomisation of patients into the two groups, there was a difference in TcPO\textsubscript{2} and Sao\textsubscript{2} between the groups at baseline. This difference, however, was significant only for TcPO\textsubscript{2}. The duration of respiratory symptoms was similar in the two groups. The results demonstrated an improvement only in the adrenaline treated group. This was found also for TcPO\textsubscript{2} even though TcPO\textsubscript{2} was lower initially in the adrenaline group.

It is probable that oedema plays a relatively larger part in the airway obstruction in infants than in older children. Several inflammatory mediators are involved, such as leukotriene C\textsubscript{4}, which increases vascular permeability and induces airway wall oedema.\textsuperscript{16} This mediator has been found in increased amounts in nasopharyngeal secretions of children with bronchiolitis and upper airway disease.\textsuperscript{17,18} It is therefore reasonable that a drug which reduces the vascular leak via a receptor stimulation might be beneficial in the treatment of acute bronchiolitis in infants and toddlers.

No serious side effects occurred during the study, but circumoral paleness that reversed shortly after cessation of the inhalation was observed in four infants receiving inhaled adrenaline, and in one infant who received placebo. Heart rate did not change significantly after inhalation of adrenaline, despite the drug's ability to cause a slight rise in blood pressure and heart rate. Similar findings have been demonstrated previously by Coupe and coworkers in adults where heart rate tended to decrease and TcPO\textsubscript{2} increased after nebulised laevorotatory adrenaline.\textsuperscript{4} Furthermore, racemic adrenaline, which is a mixture of the dextrorotatory and laevorotatory forms of adrenaline, has been claimed to have the advantage over ordinary laevorotatory adrenaline of reducing less tachycardia,\textsuperscript{19} although no pharmacological evidence for this is available. In the current study, however, a significant, although small rise in mean systolic blood pressure was observed immediately and 45 minutes after inhalation of adrenaline, but not after placebo. The small increase in systolic blood pressure observed immediately after inhalation in the group receiving adrenaline may be related to the hyperventilation and crying seen in some children during inhalation, supported by the finding of an initial rise in TcPO\textsubscript{2} and heart rate seen immediately after inhalation in both groups. The observed rise in blood pressure 45 minutes after inhalation of adrenaline may be related to drug effect.

Several studies have shown a decline in oxygen saturation or lung function in infants with bronchiolitis treated with inhaled salbutamol.\textsuperscript{13,20} However, the present study demonstrates a decrease in oxygenation in the group of infants and toddlers receiving adrenaline, as evaluated both by oxygenation and clinical score. Previous studies support this finding; in small children an increase in Sao\textsubscript{2} was found,\textsuperscript{5} and in adults with acute asthma Coupe and coworkers\textsuperscript{4} found a significant increase in arterial P0\textsubscript{2} after inhalation of nebulised adrenaline. On the other hand, Lenney and Milner\textsuperscript{3} found no improvement in airway resistance either when nebulised phenylephrine (an \(\alpha\) adrenergic stimulant) or nebulised adrenaline (\(\alpha\) and \(\beta\) adrenergic stimulant) was inhaled by children below 18 months of age. This discrepancy may be due to resistance not being the best measure of the effect of medication, as resistance of the airways in infants is greatly affected by alterations of large airway tone ("breaking").\textsuperscript{22}

Few studies have been performed to compare the effect of inhalation of a combined \(\alpha\) and \(\beta\) adrenergic to that of a selective \(\beta\textsubscript{2}\) agonist with modest local airway obstruction. Kjellman and coworkers have shown in children with asthma (aged seven-14 years), that the bronchodilating effects of 0-9 mg/kg inhaled racemic adrenaline were comparable with those of 0-15 mg/kg salbutamol.\textsuperscript{23} They speculated that the \(\alpha\) agonist activity may prevent a fall in arterial P0\textsubscript{2}, which may occur with a ventilation-perfusion mismatch occasionally seen after inhalation of a selective \(\beta\textsubscript{2}\) agonist.\textsuperscript{20}

In the present study no comparison with a \(\beta\textsubscript{2}\) agonist was performed, but the study indicates that treatment with nebulised racemic adrenaline is safe, and may be used as an alternative for symptomatic relief in infants and toddlers with acute bronchiolitis when beneficial effects of traditional bronchodilating medication are not seen.

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Y chromosome in Turner’s syndrome

Most pregnancies with a 45,X fetus end in spontaneous abortion. This fact has led to the suggestion that strict 45,X is lethal and apparent 45,X babies born alive are almost invariably mosaics.\(^1\) Using conventional cytogenetic techniques and analysing two tissues about 75% of liveborn babies with Turner’s syndrome can be shown to exhibit mosaicism.

By using the polymerase chain reaction and Southern blot analysis it is now possible to detect minute amounts of Y chromosomal material of the order of 1 in 100 000 cells. A report in the *Lancet* from Pittsburgh, Pennsylvania (Mirjana Kocova and colleagues, *Lancet* 1993; 342: 140–3) describes the use of these techniques on blood from 18 patients with Turner’s syndrome and no detectable Y chromosome on conventional cytogenetic analysis. They were able to detect small amounts of Y chromosome material in six of the 18 when testing for part of the sex determining region (SRY gene) located on the distal part of the short arm. Testing for material near the centromere (DY23) gave negative results.

The presence of Y chromosome genetic material may have important clinical implications since it may determine susceptibility to gonadal tumours especially in patients treated with growth hormone.\(^1\) Long term follow up studies of these patients are advocated.

ARCHIVIST

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