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Bronchodilator aerosol administered by metered dose inhaler and spacer in subacute neonatal respiratory distress syndrome

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Abstract

There is increasing evidence that bronchodilators are effective in ventilator dependent preterm infants. The effects of single doses of salbutamol (400 μg), ipratropium bromide (72 μg), and placebo (four puffs) given by metered dose inhaler and spacer (MDIS) were examined in 10 ventilated preterm infants, with a mean birth weight of 800 g at a postnatal age of 1 week, who were suffering from respiratory distress syndrome. The agents were each given in an open, random design. Blood gases were measured and ventilatory efficiency index (VEI) and arterial/alveolar oxygen tension ratio (Pa_{O_2}/PA_{O_2}) were calculated five minutes before and 30 minutes after administration. Heart rate and mean arterial blood pressure were noted. The mean Pa_{O_2} improved by 0·61 kPa and 0·69 kPa after salbutamol and ipratropium bromide, respectively and these changes were significantly greater than the 0·5 kPa fall seen with placebo. The mean arterial carbon dioxide tension fell by 0·98 kPa after salbutamol and 0·59 kPa after ipratropium bromide. After both salbutamol and ipratropium bromide, VEI improved significantly (by 23% and 20% respectively) but there was no significant change in the Pa_{O_2}/PA_{O_2}, suggesting that respiratory mechanics and not ventilation/perfusion balance had improved after a single dose of bronchodilator. We conclude that both salbutamol and ipratropium bromide given by MDIS have useful short term effects in ventilator dependent neonates with respiratory distress syndrome. Precise dose regimens and long term effects remain to be worked out.

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There is growing interest in the use of therapeutic aerosols for ventilated neonates.[1] Bronchodilator aerosols including β_2 agonists and anticholinergic agents have been evaluated in ventilator dependent infants with chronic lung disease.[2–6] One basis for their apparent efficacy in severe chronic lung disease is the airway smooth muscle hypertrophy,[7 8] which has been found in preterm ventilated infants with respiratory distress syndrome as early as 1 week of age.[9–11] Single doses of salbutamol and ipratropium bromide administered by jet nebuliser have been reported to improve pulmonary mechanics in ventilated infants with chronic lung disease.[2 6] However, recent in vitro and in vivo studies have shown that jet nebulisers are a less efficient means of delivering aerosol to preterm ventilated infants than metered dose inhaler and spacer (MDIS) systems.[12–14] The first report of the use of MDIS in ventilated preterm infants with early respiratory distress syndrome was very encouraging.[15]

We designed this study to examine the clinical effects of two bronchodilator agents, salbutamol and ipratropium bromide administered by MDIS, to preterm infants with respiratory distress syndrome during mechanical ventilation.

Methods

STUDY DESIGN

This was an open, randomised, placebo controlled study of single doses of each of two drugs (salbutamol and ipratropium bromide) administered at intervals of more than eight hours on two or three consecutive days. The outcomes of major interest were arterial blood gases, ventilatory efficiency index (VEI), and arterial/alveolar oxygen tension ratio (Pa_{O_2}/PA_{O_2}). The study was approved by the ethics committee of the Royal Postgraduate Medical School and written parental consent was always obtained.

STUDY POPULATION

Ventilator dependent infants were studied in the neonatal intensive care unit of Hammersmith Hospital and the Meir General Hospital, Kfar Saba, Israel (table 1). The male:female ratio was 4:6. The infants included in this study were less than 34 weeks gestational age at birth, had clinical and radiographic evidence of respiratory distress syndrome, and required mechanical ventilation at the time of study. Three had been given surfactant treatment (Curosurf, Serono) in the

Table 1 Infant characteristics at entry (n=10)

	Median (range)
Gestational age (weeks)	28 (26–34)
Birth weight (g)	880 (620–1760)
Postnatal age (days)	7 (5–12)
Postconceptional age (weeks)	29 (27–35)
Fractional inspired oxygen	0·35 (0·25–0·60)
Peak inspiratory pressure (cm H_2O)	15·5 (12–27)
Positive end expiratory pressure (cm H_2O)	3 (2–4)
Ventilator rate (per min)	35 (15–75)
Inspiratory time (sec)	0·53 (0·32–1·33)

first 48 hours of life. They were studied toward the end of the first week of life, during a period of clinical stability. No infant had evidence of shunting through a patent ductus arteriosus. No other selection criteria were used, and all of the patients who were studied are reported here. None of the infants had received bronchodilator treatment or had any significant complications at the time and all had a functional arterial cannula or catheter in place for clinical management. The infants were intubated with size 2·5 or 3 Coles pattern (shouldered) tubes (Portex).

PROCEDURE

Arterial blood (0·2 ml) was sampled from an indwelling catheter in either the umbilical artery or a radial artery, five minutes before and 30 minutes after administration of each drug, for standard blood gas measurement (Radiometer ABL-300). The changes in heart rate and directly measured, mean arterial blood pressure (Tektronix 413A Neonatal Monitor, Tektronix Inc, and in-line blood pressure transducer, MS860, Madax Medical Inc), were noted five minutes before and at 15–30 minute intervals after administration of each drug for up to 2·5 hours. VEI and Pa_{O_2}/P_{AO_2} were calculated from blood gas data to examine the response to each bronchodilator, before and 30 minutes after inhalation. VEI was calculated after the definition of Kwong *et al*[16]: $VEI = k/(f \times \Delta P \times Pa_{CO_2})$ where f is ventilator frequency, ΔP is the difference between peak inspiratory pressure and end expiratory pressure (kPa), k is a constant which is proportional to the metabolic rate, and Pa_{CO_2} is the carbon dioxide tension in kPa. The constant k was assigned a value of 500,[16] but the precise number is irrelevant in practice. Pa_{O_2}/P_{AO_2} was calculated using the formula: $Pa_{O_2}/P_{AO_2} = Pa_{O_2}\ (95 \times F_{IO_2}) - Pa_{CO_2}$ where blood gas values are in kPa and F_{IO_2} is fractional inspired oxygen (expressed as a fraction).

AEROSOL ADMINISTRATION

We used a small volume spacer (Aerochamber MV15, Trudell Medical) with a diameter of 4·1 cm, a length of 11·0 cm, a volume of 145 ml and a 15 mm endotracheal tube connector. Metered dose inhalers of salbutamol (Glaxo, 100 μg/puff) and ipratropium bromide (Boehringer Ingelheim, 18 μg/puff) or placebo (Glaxo, comprising propellants and lubricants but omitting the active agent) were shaken and inserted into the Aerochamber spacer. The spacer was filled with oxygen and was connected via a manual puffer to an oxygen supply at 8 l/min with an appropriately set blow off valve. Four individual puffs (400 μg of salbutamol, 72 μg of ipratropium bromide) were delivered at end expiration with five manual breaths between each puff. Routine endotracheal tube suction was not performed for 2·5 hours after administration of each drug, and in fact no subject required suction during this interval. The interval between successive drugs was at least eight hours and the order was predetermined using a random number table.

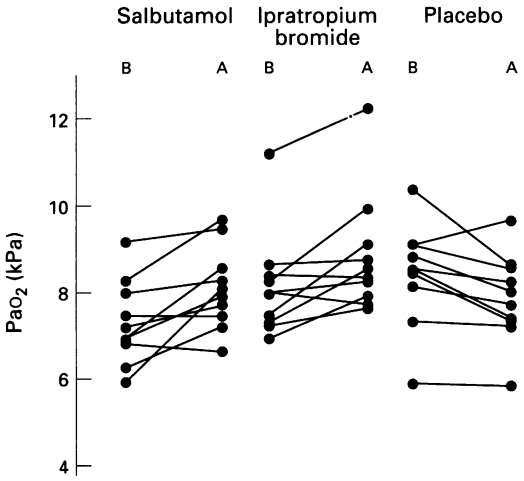

Figure 1 Individual values of Pa_{O_2} before (B) and 30 minutes after (A) inhalation of each drug.

STATISTICAL ANALYSIS

For blood gas, VEI, and Pa_{O_2}/P_{AO_2} data within each drug group, values before and after the dose (log transformed for VEI and Pa_{O_2}/P_{AO_2}) were analysed using paired *t* test and a p value $<0·05$ was considered statistically significant. Analysis of variance was used to compare values between drugs, and between time points within drug groups. In the former case, the drugs were regarded as a within subjects factor, and in the latter case, the time points were regarded as a within subjects factor. Individual comparisons were made using *t* tests based on results of the analysis of variance, using the mean square error and error degree of freedom. The Bonferroni correction was used where appropriate.

Because of the small numbers of subjects involved, factorial analysis to assess the possible influence of gestational age, mode of delivery, surfactant treatment and other variables, was not attempted.

Results

There was no significant difference in the baseline values of blood gases, VEI, or Pa_{O_2}/P_{AO_2} between salbutamol, ipratropium bromide, and placebo studies.

After inhalation of salbutamol and ipratropium bromide 8/10 infants showed increases in Pa_{O_2} at 30 minutes (fig 1), resulting in significant mean increases of 0·61 kPa and 0·69 kPa respectively ($p<0·05$, table 2). These changes were significantly greater than the mean fall in Pa_{O_2} of 0·55 kPa seen after placebo ($p<0·017$). In 8/10 infants Pa_{CO_2} fell 30 minutes after inhaled salbutamol (fig 2), a significant mean decrease of 0·98 kPa ($p<0·05$, table 2). Again this change was significantly greater than the fall of 0·02 kPa seen with placebo ($p<0·017$). Although inhaled ipratropium bromide produced a mean decrease in Pa_{CO_2} of 0·59 kPa, this was not significantly different from the preinhalation

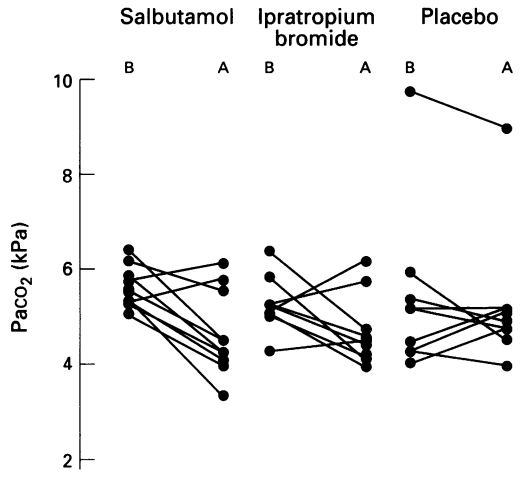

Figure 2 Individual values of $PaCO_2$ before (B) and 30 minutes after (A) inhalation of each drug.

value (table 2), but significantly greater than the change after placebo ($p<0.017$). The effects of salbutamol and ipratropium bromide on PaO_2 and $PaCO_2$ did not differ significantly.

Neither salbutamol nor ipratropium bromide resulted in an increase in PaO_2/PAO_2 above their baseline values, and the effect of salbutamol and ipratropium bromide did not differ compared with placebo or compared with each other. Salbutamol caused a significant increase in VEI of 23·4% ($p<0.05$, table 3; fig 3), significantly greater than the fall of 1·67% seen after placebo ($p<0.017$). Ipratropium bromide resulted in a significant increase in VEI of 19·8% ($p<0.05$, table 3; fig 3), although in comparison with placebo, this difference was not significant. The changes in VEI with salbutamol and ipratropium bromide did not differ from each other.

Clinically significant tachycardia, hypotension, or hypertension were not induced in any infant for 2·5 hours after inhalation of salbutamol and ipratropium bromide. The heart rate 30 minutes after inhaled salbutamol was, however, significantly greater than at baseline and the tachycardia appeared to last for two hours (fig 4), with a maximum mean increase in heart rate of 23 beats/min, 30–60 minutes after administration (fig 4). After inhaled ipratropium bromide, a smaller increase in heart rate of 14 beats/min was noted at 45 minutes after inhalation (fig 4). In comparison with changes in heart rate after placebo, salbutamol produced significant increases at 60–90 minutes ($p<0.007$), but the changes in heart rate with ipratropium bromide did not differ from placebo effects. After inhaled salbutamol and ipratropium bromide, the maximum increases in heart rate were observed at median times of 53 and 83 minutes respectively. Salbutamol and ipratropium bromide had no significant effect on mean arterial blood pressure for 2·5 hours after inhalation.

Table 2 Arterial blood gases and pH

	Mean (range) baseline values	*Mean (95% confidence interval) change at 30 minutes*
pH		
Salbutamol	7·30 (7·21–7·41)	0·05 (0·03 to 0·07)*
Ipratropium bromide	7·32 (7·25–7·41)	0·04 (0·01 to 0·06)*
Placebo	7·30 (7·26–7·36)	0·02 (−0·01 to 0·04)
PaO_2 (kPa)		
Salbutamol	7·30 (5·92–9·15)	0·61 (0·04 to 1·33)*
Ipratropium bromide	8·14 (6·95–11·20)	0·69 (0·21 to 1·17)*
Placebo	8·41 (5·88–10·38)	−0·55 (−1·01 to −0·08)
$PaCO_2$ (kPa)		
Salbutamol	5·63 (5·07–6·40)	−0·98 (−1·60 to −0·36)*
Ipratropium bromide	5·25 (4·27–6·40)	−0·59 (−1·25 to 0·08)
Placebo	5·27 (4·00–9·73)	−0·02 (−0·57 to 0·53)

*Change at 30 minutes significant at $p<0.05$.

Table 3 VEI and PaO_2/PAO_2

	Mean (range) baseline values	*Mean (95% confidence interval) % change at 30 minutes*
VEI		
Salbutamol	0·27 (0·07–0·63)	23·40 (9·22 to 37·57)*
Ipratropium bromide	0·30 (0·06–0·83)	19·78 (1·82 to 37·74)*
Placebo	0·42 (0·12–1·06)	−1·67 (−11·88 to 8·55)
PaO_2/PAO_2		
Salbutamol	0·26 (0·10–0·45)	7·79 (−2·00 to 17·58)
Ipratropium bromide	0·28 (0·11–0·46)	5·59 (−0·41 to 11·59)
Placebo	0·36 (0·13–0·69)	−4·45 (−12·52 to 3·61)

*Change at 30 minutes significant at $p<0.05$, in terms of log data.

Discussion

We found that in 1 week old preterm, ventilated infants with respiratory distress syndrome, both salbutamol and ipratropium bromide given by MDIS had beneficial effects on blood gases and ventilatory efficiency, 30 minutes after administration. Improvements in oxygenation were not accompanied by significant changes in the PaO_2/PAO_2 ratio, suggesting that mechanical effects leading to an improvement in ventilatory function rather than alterations in the matching of ventilation and perfusion were responsible for the improvement in PaO_2. The degree of improvement, although modest and measured at only one time point, can be considered clinically significant and suggests that further exploration of the role of bronchodilators early in the course of respiratory distress syndrome would be profitable.

We decided to study infants at an early stage because of increasing evidence of the efficacy of bronchodilators early in the development of chronic lung disease of prematurity.[5 15] Although the acute inflammatory changes of respiratory distress syndrome in the first week of life might appear to be infertile ground for bronchodilators, there are several reasons to suppose that these agents could have a useful role. Firstly there is evidence of airway smooth muscle hypertrophy in the airways of infants with respiratory distress syndrome as early as one week after birth[9–11] and secondly, mediators released from airway inflammatory cells may act directly or indirectly (via neural reflexes) to cause increased smooth muscle contraction.[8]

In some reports, no change has been observed in either transcutaneous partial pressure of oxygen,[3 5] or oxygen saturation by oximetry[6] after bronchodilator administered by jet nebuliser. The improvement in PaO_2 that we found seems more likely to result from the more efficient method of administration of the drugs and the avoidance of the cold droplets associated with jet nebulisation.

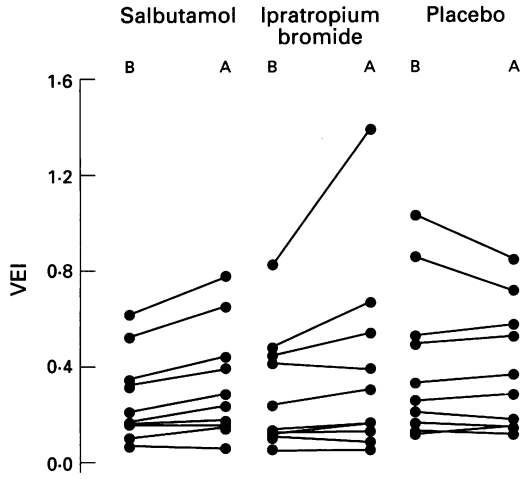

Figure 3 Individual values of the VEI calculated from the arterial blood gas data before (B) and 30 minutes after (A) inhalation of each drug.

We chose to administer the drugs by MDIS because of the efficiency of this system in comparison with jet nebulisers[13 14] and because of the ease of administration. Disconnection from the ventilator to administer the metered dose inhaler, although undesirable, had no ill effects apart from brief and minor hypoxaemia. The doses used were estimated from direct pulmonary deposition data using soluble drugs.[13] Using the MDIS in ventilated neonates, we found a mean pulmonary deposition of sodium cromoglycate of 1·72%.[13] If this figure is applied to the present study, then the pulmonary doses of salbutamol and ipratropium bromide were about 7 μg (8 μg/kg) and 1·3 μg (1·4 μg/kg) respectively. These are of the same order as doses of nebulised agents given to children with acute severe asthma. The prolonged tachycardia after salbutamol might suggest that the dose was rather high. In a preliminary study of six subjects that we carried out under identical circumstances, a dose of salbutamol of 200 μg (two puffs) had no detectable effect on mean heart rate but a similar mean effect (0·87 kPa) on Pa_{O_2}. We chose to use four puffs in the present study so that only a single placebo inhaler was needed for comparison with both salbutamol and ipratropium bromide. Dose ranging studies are clearly needed, as suggested by the work of Denjean *et al.*[15]

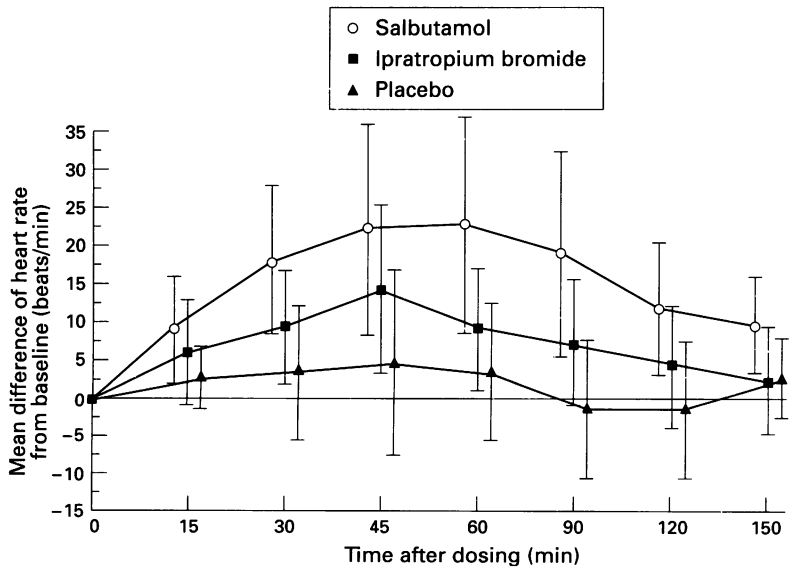

Figure 4 Mean changes in heart rate at each time interval for 2·5 hours after inhalation of salbutamol, ipratropium bromide, and placebo with reference to baseline value. The bars indicate 95% confidence intervals of mean difference. The changes at 60–90 minutes after inhaled salbutamol differed significantly from those seen after placebo.

While jet nebulisation has several undesirable effects, including cooling of the inspired gas, deterioration in humidification,[17 18] loss of most of the aerosol by the continuous gas flow,[19] and deposition of drug in the ventilator circuit,[20] MDIS is potentially easier to use as it requires no auxiliary gas flow and several doses may be rapidly given.[14]

VEI is a useful index with which to compare respiratory status among ventilated infants in the absence of spontaneous breathing.[16] It may be less accurate in the presence of spontaneous breathing as in this study. Because ventilator input varies from patient to patient, direct comparison of Pa_{CO_2} between patients does not reflect differences in lung function.[16] This is the reason that VEI was developed, although strictly speaking, as ventilatory support was not altered during the 30 minute observation period in the present study, it did not add to the within subject comparison of changes in Pa_{CO_2}. The ratio between tidal volume delivered and the ventilator driving pressure (respiratory system compliance) would be one measure of ventilatory efficiency, but accurate prolonged measurement requires carefully calibrated equipment. Instead VEI provides a surrogate for respiratory system compliance which takes into account variation in Pa_{CO_2}.[16] It may also be affected by changes in deadspace and respiratory quotient as its main assumption is that metabolic rate (hence carbon dioxide production) is constant over the period of study. This may be untrue after salbutamol treatment, which could lead to an increase in metabolic rate. If this were the case, then the measured improvement in VEI after salbutamol would have been underestimated. In the present study, VEI increased significantly after both salbutamol and ipratropium bromide, suggesting that pulmonary mechanics and hence the efficiency of alveolar ventilation had improved. This conclusion must be tempered by the possibility that spontaneous breathing effort may have increased after bronchodilator treatment.

The increase in ventilatory efficiency (and presumably alveolar ventilation) after bronchodilation lead to a fall in alveolar carbon dioxide tension (Pa_{CO_2}) and therefore to Pa_{CO_2}. A commensurate increase in P_{AO_2} would then explain the increase in Pa_{O_2} which we found. The Pa_{O_2}/P_{AO_2} ratio did not alter significantly, so that ventilation/perfusion balance was not greatly affected by salbutamol or ipratropium bromide.

Selective β adrenoreceptors are plentiful in the lung periphery and small airways especially in the epithelium,[21] while muscarinic receptors are numerous in the smooth muscle of the larger airways of adult subjects.[22] There are no data for preterm neonates, but the potential

additive effects of salbutamol and ipratropium bromide might usefully be investigated in neonates.

A word of caution seems appropriate in relation to the changes in airway elastance that might be induced by bronchodilators. The work of Shaffer's group in preterm lamb airways, has demonstrated the susceptibility of tracheal segments to distortion by mechanical ventilation.[23] By reducing the elastance of the airways, by removing any support that might be rendered by the tone of the airway smooth muscle, it is possible that deformability might increase, with adverse long term consequences. This has yet to be established in either animal or human lungs in vivo, but should caution against the extrapolation of this single dose study to the long term use of bronchodilators.

It is also important to draw attention to the unknown adverse effects on preterm infants of the propellants and surfactants present in MDIS devices. The small decline in PaO_2 after the placebo given by MDIS, without alteration in $PaCO_2$, may have been due to these agents.

We conclude that salbutamol and ipratropium bromide given by a small volume spacer (Aerochamber) during intermittent positive pressure ventilation, had a beneficial short term effect on gas exchange and ventilatory efficiency in subacute respiratory distress syndrome in preterm infants without any clinically significant side effects. However, we need further to evaluate the effects of bronchodilator aerosols given by MDIS to infants at various stages and with various degrees of severity of respiratory distress syndrome and chronic lung disease. Dose ranging studies, the effect of drug combinations and the effect of multiple doses are all worthy of investigation. Both the short term outcome, such as a reduction in the need for mechanical ventilation, and the long term benefit of survival free of chronic lung disease should be measured.

We are grateful to the nursing staff of the neonatal unit, Hammersmith Hospital for their patience and to Trudell Medical for the supply of Aerochambers. Dr Tzipora Dolfin was kind enough to allow the study to be completed at the neonatal unit, Meir General Hospital, Kfar Saba, Israel.

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