Ipratropium bromide delivered by metered-dose aerosol to infant wheezers

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Summary

Two methods of administration of ipratropium bromide (Atrovent; Boehringer Ingelheim) to wheezing children < 25 months of age were compared: (*i*) the conventional nebulisation (15 children); and (*ii*) a metered-dose aerosol plus spacer and mask (MDA group, 17 children). The drug induced a significant and similar fall in respiratory rate in both groups. Transcutaneous carbon dioxide pressure was also reduced significantly but was more marked in the MDA group. This increase in alveolar ventilation was similar in those < 12 months as in older children; in those with recurrent or with first time wheezing; and in those with radiological evidence of pneumonia. Clinical assessment of bronchospasm and recession was recorded as improved in over 80% of both groups. The MDA delivery of ipratropium bromide was as effective as nebulisation and was more convenient, since it required less time and equipment. It was also well accepted by the small patients.

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Wheezing is common in infants and toddlers. Hyperactive airways may be secondary to respiratory infections, including bronchiolitis, or to asthma. The therapeutic dilemma is twofold: what drugs are helpful, and by what route should they be administered. Nebulisation is a safe and effective means of delivery but β_2-agonist bronchodilators have minimal effect on clinical features or lung function until the patient is 18 - 20 months.[1,2]

However, an anti-cholinergic drug, ipratropium bromide (Atrovent; Boehringer Ingelheim), when nebulised in a dose of 250 μg improved lung function in 40% of wheezing children, many under the age of 1 year and some of whom wheezed from acute bronchiolitis.[2-4] The drug has a high maximum safe concentration so overdosage is not a hazard.

Recently, bronchodilators delivered to infants and children via a metered-dose aerosol and spacer with face mask have been shown to be effective.[5-7]

This study was designed to confirm the efficacy of the metered aerosol method compared with nebulisation of ipratropium bromide when given to wheezing infants and toddlers. The former method is convenient for primary health care facilities or home use, since it does not depend upon the availability of the nebuliser apparatus or a gas or electricity source.

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Patients and methods

Children aged 3 - 36 months were selected by medical officers in an outpatients facility if they were wheezing and had recession, a respiratory rate > 60/min at < 24 months and > 50/min at > 24 months of age, and had not received a bronchodilator in the previous 6 hours.

The children were allocated randomly to one of the following treatment regimens: (*i*) ipratropium bromide inhalant solution 250 μg (1 ml) in 2 ml of saline delivered by an electrically driven nebuliser and a hand-held mask (NEB group); and (*ii*) ipratropium bromide metered-dose aerosol (20 μg/puff), 10 puffs given over 2 - 3 minutes delivered through a face mask attached to a spacer (MDA group) (Fig. 1).

Both regimens were repeated after 1 hour and, if necessary, further hourly doses were given at the discretion of the attending medical officer.

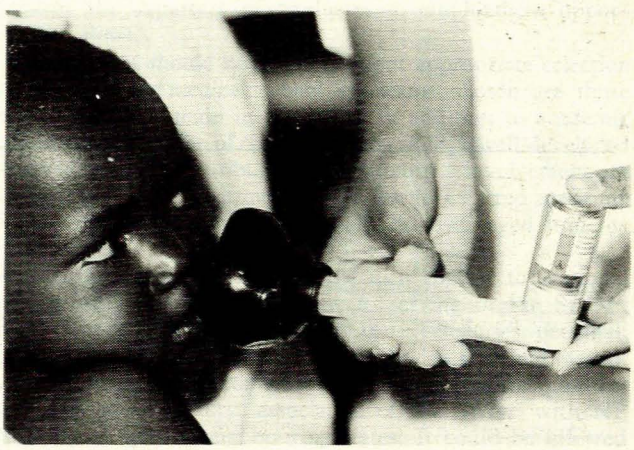

Fig. 1. Metered-dose aerosol administered with spacer and face mask.

Observations (by F.P.) were recorded on admission to the study and 1 hour after each dose: (*a*) clinical: (*i*) recession grade I — intercostal and subcostal, recession grade II — grade I plus tracheal tug and sternal recession; (*ii*) wheezing grade I — scanty and intermittent, wheezing grade II — constant and polyphonic; and (*iii*) pulse and respiratory rates. (*b*) Transcutaneous carbon dioxide pressure ($PtCO_2$) and oxygen saturation (SaO_2) measurements by pulse oximetry (FasTrac, Sensor Medics) were available for two-thirds of the patients (standardisation of the apparatus was performed before application to each patient).

Statistical methods. The paired *t*-test was employed for comparisons between time intervals of each parameter. A two-way analysis of variance was performed to establish differences between groups, age and the interaction between group and age. The effect of pneumonia and recurrence of wheezing was tested by the four-fold test.

Results

Thirty-two children were studied (median age 6 months; only 1 child > 20 months). The characteristics of the children are shown in Table I. Just over half had a prior history of wheezing, 22% had grade II (severe) bronchospasm, and 5 had radiological pneumonic shadowing. There was no significant difference between the characteristics of the MDA and NEB groups.

TABLE I. CHARACTERISTICS OF PATIENTS IN THE TWO GROUPS

	NEB	MDA	Total
No. of patients	**15**	**17**	**32**
Median age (mo.)	**6**	**7**	**6**
Boys	**8**	**13**	**21**
Recurrent wheeze	**7**	**11**	**18**
FH asthma*	**8**	**5**	**13**
Bronchospasm grade II†	**2**	**5**	**7**
Pneumonia	**2**	**3**	**5**
Admitted to hospital	**0**	**1**	**1**

* Family history of asthma present.
† See text for explanation.

After 2 doses of ipratropium bromide all but 3 children were considered well enough by their physicians to go home. One child in each group had an extra dose before discharge and 1 child in the MDA group required admission to hospital despite 4 doses.

Where clinical features of bronchospasm and recession changed from grade I or II to a better grade, improvement was documented (Table II). In the total patient population bronchospasm improved in 91% and recession in 81%, and there were no differences between the two medication groups.

TABLE II. EFFECT OF IPRATROPIUM BROMIDE ON CLINICAL FEATURES

	NEB (%)	MDA (%)	Total (%)
Recession improved	**87**	**76**	**81**
Bronchospasm improved	**93**	**88**	**91**

Table III shows the effect of the drug on all 32 children. After 2 hours (in 3 patients after 3 - 4 hours) the mean values for the respiratory rate had fallen significantly ($P = 0{,}0001$); as had the $PtCO_2$ ($P = 0{,}0001$) and pulse rate ($P = 0{,}0071$).

When the delivery systems were compared (Table IV) both methods were shown to reduce the respiratory rate and $PtCO_2$.

In the NEB group the mean values for the respiratory rate before and after the drug were significantly different ($P < 0{,}002$). The fall in respiratory rate in the NEB group ($-18 \pm 12\%$) and in the MDA group ($-19 \pm 12\%$) were significantly different from zero ($P = 0{,}0001$).

The mean values for $PtCO_2$ before and after the drug were significantly different in the MDA group ($P < 0{,}05$). A significant fall in $PtCO_2$ was induced both by nebulisation ($-8 \pm 8\%$; $P = 0{,}0118$) and by MDA ($-19 \pm 14\%$; $P = 0{,}0029$), the change being greater in the MDA patients ($P = 0{,}0770$).

A significant fall in pulse rate was restricted to the MDA group ($-8 \pm 10\%$; $P = 0{,}0001$). The effect of the drug on SaO_2 was minimal in both groups.

In the four parameters measured, the effect of the drug was the same in children aged ⩽ 12 months as those > 12 months. Figs 2 and 3 show respiratory rate and $PtCO_2$ expressed as percentage change plotted against age: a decrease of ⩾ 15% occurred in respiratory rate in 56% and in $PtCO_2$ in 45% of children.

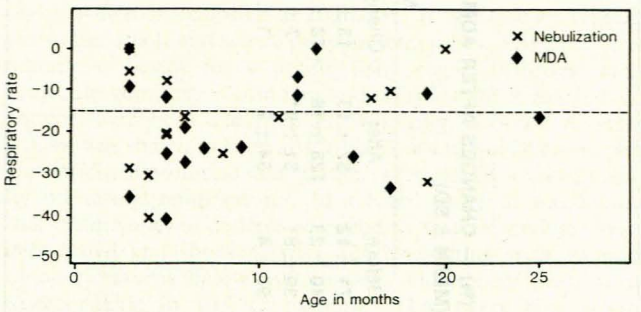

Fig. 2. Percentage change in respiratory rate induced by ipratropium bromide, related to age.

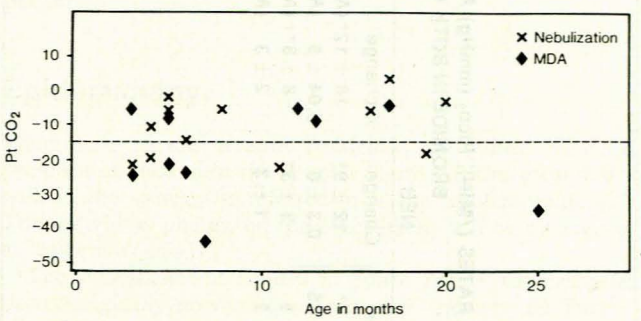

Fig. 3. Percentage change in $Ptco_2$ induced by ipratropium bromide, related to age.

The fall in respiratory rate and $PtCO_2$ was quantitatively the same in children with recurrent compared with first-time wheezing, and in those with and without radiological pneumonia.

TABLE III. EFFECT OF IPRATROPIUM BROMIDE ON TOTAL STUDY GROUP (MEAN ± SD)

	Before	After†	Change	% change
Pulse rate ($N = 32$)	**136 ± 20***	**129 ± 15***	**−7 ± 13**	**−4 ± 9**
Respiratory rate ($N = 32$)	**69 ± 9****	**56 ± 11****	**−13 ± 8**	**−18 ± 12**
Sao_2 ($N = 22$)	**93 ± 3**	**95 ± 2**	**1 ± 3**	**1 ± 3**
$Ptco_2$ ($N = 22$)	**38 ± 7*****	**32 ± 7*****	**−5 ± 4**	**−13 ± 12**

* $P = 0{,}0071$.
** $P = 0{,}0001$.
*** $P = 0{,}0001$.
† After 2 - 4 doses.

TABLE IV. RESPIRATORY AND PULSE RATES (/MIN), $Ptco_2$ (mmHg) AND Sao_2 (%) — CHANGES AFTER ADMINISTRATION OF IPRATROPIUM BROMIDE IN BOTH GROUPS (MEAN ± SD)

	NEB				MDA			
	Before	After	Change	% change	Before	After	Change	% change
Respiratory rate	68 ± 7*	55 ± 7*	−12 ± 9†	−18 ± 12† (*N* = 15)	71 ± 12	57 ± 13	−13 ± 8†	−19 ± 12† (*N* = 17)
Pulse rate	131 ± 15	130 ± 15	−0,3 ± 6	−0,04 ± 5 (*N* = 15)	140 ± 23	128 ± 16	−13 ± 15†	−8 ± 10† (*N* = 17)
$Ptco_2$	37 ± 6	33 ± 5	−3 ± 3*	−8 ± 8*† (*N* = 12)	39 ± 8*	31 ± 9*	−7 ± 4*	−19 ± 14*† (*N* = 10)
Sao_2	94 ± 3	95 ± 2	1 ± 3	2 ± 3 (*N* = 12)	93 ± 4	94 ± 2	1 ± 2	1 ± 3 (*N* = 10)

* Significantly different from each other.
† Significantly different from zero.
For individual *P* values, see text.

Discussion

In this study ipratropium bromide could be shown by simple monitoring methods to benefit some wheezing infants < 25 months of age. Following administration there was a significant fall in both respiratory rate and $Ptco_2$ ($P = 0{,}0001$). Since arterial (and therefore $Ptco_2$) and alveolar carbon dioxide pressures are linearly related, the fall in $Ptco_2$ reflected an increased alveolar ventilation. This would follow either a rise in respiratory frequency or an increase in tidal volume. The first option did not occur. This improvement in alveolar ventilation was significantly greater in the MDA group than in the NEB group ($P = 0{,}0370$).

Meaningful benefit from the drug, if judged by a ⩾ 15% decrease, occurred in the $Ptco_2$ of 10 of 22 children (45%) and in the respiratory rate in 56%. Further, children < 12 > months reacted similarly (Figs 2 and 3), and the response was not affected by the presence of radiological lower-respiratory tract infection or a history of previous wheezing.

Sao_2 was not altered by the drug and tachycardia was reduced only in the MDA group ($P = 0{,}0034$).

In other studies of ipratropium bromide in bronchiolitics and wheezing children < 3 years of age, work of breathing, airway resistance and total respiratory resistance were improved in 40% of cases, with response demonstrated in those < 1 year.[2,3] The mechanism of action is probably a decrease in central airway resistance, while peripheral airway function is unchanged.[3,4]

The clinical parameters of recession and bronchospasm were judged to have improved in over 80% of children, with similar results in both groups. This is a better clinical response than reported previously in bronchiolitis and infantile asthma.[8,9]

Delivery of the drug by an MDA with spacer and face mask produced effects comparable to the well-tried nebulisation method, the mean improvement in alveolar ventilation in fact being greater in the MDA group ($P = 0{,}0370$).

Our data can be added to those of more sophisticated studies that conclude that ipratropium bromide benefits a useful percentage of young children with hyperreactive airways. Delivery of the drug via an MDA obviates the need for expensive nebulisation apparatus and extends the use of this treatment modality to primary health care facilities that would normally not offer it. Substitution of a polystyrene cup for the spacer and mask would permit continuation of treatment in the home. The technique was easily mastered by mothers and was well accepted by the infants.

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