

# Metered dose inhaler and nebuliser in acute asthma

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## Abstract

One hundred and eleven children with acute asthma were studied to compare delivery of terbutaline by either a metered dose inhaler (MDI) with a valved holding chamber or a nebuliser driven by air. Eligible patients were randomised; the MDI group received three puffs (0.75 mg) of terbutaline and the nebuliser group received 2 ml (5.0 mg) terbutaline solution diluted with 2 ml 0.9% saline for inhalation over 10 minutes. Patients were evaluated by spirometry, pulse oximetry, and clinical severity scoring system at baseline and again 15 minutes after the beginning of treatment. The baseline data of the two groups were not significantly different. All parameters of spirometry, except the peak expiratory flow (PEF) for the nebuliser group, and clinical severity score for both groups significantly improved after terbutaline treatment. Compared with the nebuliser group, the MDI group after treatment had better mean (SD) oxygen saturation ( $\text{SaO}_2$ ; 96.82 (1.63)% *v* 95.44 (1.88)%), frequency of oxygen desaturation (23.2% *v* 47.3%), absolute increase of PEF (32.6 (37.7) l/min *v* 10.2 (34.7) l/min), and  $\text{SaO}_2$  (0.54 (1.64)% *v* -0.47 (1.84)%). There was also a mean (SD) per cent increase of forced expiratory volume in one second (22.9 (21.0)% *v* 15.4 (16.1)%), PEF (27.7 (38.4)% *v* 7.7 (25.1)%), and  $\text{SaO}_2$  (0.58 (1.72)% *v* -0.47 (1.93)%). In conclusion, aerosol treatment by MDI (with a valved holding chamber) in this study proved to be superior to nebuliser treatment in terms of  $\text{SaO}_2$  and some measurements of spirometry. Respiratory therapists working with children with severe asthma should be aware of the possibility of oxygen desaturation, especially when using room air as the driving gas for nebulisation.

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At present inhaled selective  $\beta_2$  adrenergic agonists have largely replaced the injection of adrenaline and have become the mainstay of treatment for acute asthma because they show fewer side effects and equivalent bronchodilation.<sup>1-3</sup> These aerosols may be administered by metered dose inhaler (MDI) or nebuliser, thus not only reducing the adverse effects from oral or parenteral administration, but also avoiding patient discomfort when treating a paediatric population.

Although effective, the use of nebulised  $\beta_2$  agonists has various disadvantages. Nebulisers are expensive, cumbersome to use, and need outside electric power. The MDI is a convenient device to use for quick relief of acute airway obstruction, but there can be problems of coordination between actuation and inhalation, particularly in small children who may not comprehend the instructions or whose hand-inspiration coordination may not yet be adequately developed.<sup>4,5</sup> Attachment to a pressurised  $\beta_2$  aerosol of a holding chamber with a one way valve system has been shown to increase the deposition of aerosol particles in the lungs and decrease upper airway aerosol deposition, as does unaided use of an MDI.<sup>6,7</sup> This development has resolved many of the technical problems that commonly occurred in asthmatic children using an unaided MDI for treatment.

Some recent reports have suggested there is little difference between the MDI and nebuliser methods of treatment in asthmatic patients.<sup>8-13</sup> Most of these reports measured only forced vital capacity (FVC) and forced expiratory volume in one second ( $\text{FEV}_1$ )<sup>8-11</sup>; several reports also measured the dyspnoea score.<sup>12,13</sup> All of the studies used oxygen as the driving gas in nebuliser treatment, and therefore the oxygen saturation ( $\text{SaO}_2$ ) between the two methods was not comparable because no oxygen was supplied in MDI treatment. It is important that  $\text{SaO}_2$  is measured because, although there have been a few reports describing the occurrence of hypoxaemia or oxygen desaturation after inhalation of selective  $\beta_2$  adrenergic agonists,<sup>3,14,15</sup> oxygen is not routinely given in nebuliser treatment of acute asthmatics here or in many other paediatric emergency institutions,<sup>16</sup> even for those with severe asthma. Also it is usually cumbersome and sometimes dangerous to provide oxygen at home because of inflammability. To our knowledge,  $\text{SaO}_2$  has not been studied when room air is used as the driving gas for both treatments.

This study used a clinical scoring system, spirometer, and pulse oximeter to compare the clinical response,  $\text{SaO}_2$ , and bronchodilator response to terbutaline as delivered by an MDI (with a valved holding chamber) or an air compressor nebuliser driven by room air in asthmatic children with acute attacks.

## Patients and methods

### PATIENTS

Patients who presented to the emergency department and paediatric allergy clinic of the Taipei Municipal Chung Hsiao Hospital with

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a diagnosis of acute asthma, or of acute exacerbation of chronic asthma, were enrolled in the study. The diagnosis of asthma was based on American Thoracic Society standards.<sup>17</sup> Patients were eligible for study if they were at least 5 years of age and able to perform spirometry. Patients with complications of pneumonia, congestive heart failure, foreign body aspiration, or bronchopulmonary dysplasia were excluded. Patients who had received any aerosolised  $\beta$  agonist within six hours before presentation were also excluded.

#### TREATMENT PROTOCOLS

The inhalation treatment was performed after measurements of baseline spirometry,  $\text{SaO}_2$ , pulse rate, and clinical severity scores. The MDI and nebuliser treatments alternated with each other, week by week, for successive eligible patients. The MDI group received three puffs (0.75 mg) of terbutaline (Bricanyl, Astra) inhaled through a holding chamber with facemask (AeroChamber, Trudell Medical). Patients were taught to take three deep breaths after each actuation. The nebuliser group received 2.5 mg (2 ml) of terbutaline solution (Bricanyl, Astra) diluted with 2 ml normal saline (4 ml in total) delivered by an air compressor nebuliser (Pulmo-Aide, Model No 5610D; DeVilbiss), driven by air at a flow rate of 8 l/minute, inhaled through a mouthpiece. Patients were instructed to take three deep breaths slowly. When tapping the solution container did not result in further aerosolisation, the mouthpiece was removed from the patient. This procedure usually took 10 minutes. Measurements of baseline spirometry,  $\text{SaO}_2$ , pulse rate, and clinical severity scores were repeated 15 minutes after the beginning of the inhalation treatment.

#### MEASUREMENTS

##### Spirometry

All eligible patients had spirometry performed including FVC,  $\text{FEV}_1$ , peak expiratory flow (PEF), and forced expiratory flow 25–75% ( $\text{FEF}_{25-75\%}$ ). All tests were performed using standard spirometry (Vitalograph Compact, Cat No 42.000; Vitalograph). The FVC,  $\text{FEV}_1$ , PEF, and  $\text{FEF}_{25-75\%}$  values of at least

three consecutive efforts were determined using the curve having the best  $\text{FEV}_1$  as defined by the American Thoracic Society.<sup>18</sup> The values were expressed as percentage of the predicted normal values for height and sex.

##### $\text{SaO}_2$ and pulse rate

$\text{SaO}_2$  and pulse rate were recorded using a pulse oximeter (model Accusat, Datascope) and measured through the nail bed of the index finger.  $\text{SaO}_2$  values were accepted only if they were stable for 5 seconds on the pulse oximeter screen during reading.

##### Evaluation of clinical response

The clinical severity scores of patients were evaluated according to Tal *et al.*<sup>19</sup> The parameters included respiratory rate, wheezing, cyanosis, and accessory respiratory muscle utilisation. Each item was scored from 0–3 and evaluated by the same paediatrician. The scores were then added to give a single clinical severity score.

#### STATISTICS

Results were expressed as mean (SD). The two tailed Wilcoxon signed rank sum test was used for statistical analysis of the clinical severity scores. The two tailed Student's *t* test was used for statistical analysis of spirometry and pulse oximetry at baseline and after treatment, with mean absolute and per cent increases from baseline. Paired tests were used within the same groups and unpaired tests, between groups. The sex and medication and comparative frequency of the decrease of  $\text{SaO}_2$  after treatment were assessed by the  $\chi^2$  test. A *p* value of less than 0.05 was considered statistically significant.

#### Results

One hundred and seventeen patients initially enrolled into this study were randomised into the two groups (60 to the MDI, 57 to the nebuliser). Six patients did not complete the study: four in the MDI group were withdrawn because they were either frightened by being covered with the AeroChamber mask or unable to comply with mouth breathing instructions and two in the nebuliser group were excluded because they refused to inhale the foggy aerosol. Table 1 shows demographic characteristics of the 111 patients completing the study. Patients randomised to the two groups were well matched at baseline for age, sex, FVC,  $\text{FEV}_1$ , PEF,  $\text{FEF}_{25-75\%}$ ,  $\text{SaO}_2$ , pulse rate, and clinical severity score.

The results from both groups, after terbutaline treatment, are shown in table 2. All parameters (except the PEF for the nebuliser group) of spirometry and clinical severity score for both groups significantly improved after terbutaline treatment, as did the  $\text{SaO}_2$  for the MDI group. The mean value of  $\text{SaO}_2$  for the nebuliser group decreased after treatment but was not statistically significant ( $p=0.0627$ ).

Table 1 Demographic characteristics of patients before treatment; values are mean (SD)

	MDI group (n=56)	Nebuliser group (n=55)
Sex (M/F)	40/16	35/20
Age (years)	8.1 (2.6)	8.4 (3.0)
Range	5–16	5–15
No who had taken oral bronchodilators before study*	14	16
Duration of symptoms (days)	3.05 (2.20)	3.12 (2.17)
FVC (%)	74.75 (24.31)	71.63 (21.24)
$\text{FEV}_1$ (%)	65.74 (20.33)	63.14 (20.50)
PEF (%)	57.56 (19.60)	60.30 (21.32)
$\text{FEF}_{25-75\%}$ (%)	57.53 (28.02)	55.63 (28.77)
Clinical severity score	4.86 (1.80)	4.60 (1.83)
$\text{SaO}_2$ (%)	96.29 (1.94)	95.91 (1.96)
Pulse rate (beats/min)	110 (19)	111 (20)

\*Still within the pharmacological effect of the drugs.  
The spirometric data are expressed as % predicted value.

Table 2 Clinical and laboratory parameters after treatment; values are mean (SD)

	MDI group	Nebuliser group	p Value†
FVC (%)	86.60 (24.51)*	82.02 (22.80)*	NS
FEV <sub>1</sub> (%)	78.80 (21.58)*	71.80 (22.08)*	NS
PEF (%)	70.10 (21.24)*	62.79 (20.25)	NS
FEF <sub>25-75%</sub> (%)	75.24 (31.25)*	63.82 (28.83)**	NS
Clinical severity score	2.27 (1.83)*	2.53 (1.93)*	NS
SaO <sub>2</sub> (%)	96.82 (1.63)***	95.44 (1.88)	<0.0001
Pulse rate (beats/min)	111 (17)	113 (19)	NS

NS: not significant.

†p Value computed by two tailed unpaired Student's *t* test.

\*p<0.0001, \*\*p=0.0010; \*\*\*p=0.0177 when compared with values of the same group before treatment by paired Student's *t* test.

The mean pulse rate showed almost no change. Compared with the MDI group, the SaO<sub>2</sub> of the nebuliser group after treatment was significantly lower. Otherwise, there was no statistically significant difference between the two groups in spirometry, clinical severity score, or pulse rate.

Table 3 demonstrates the mean absolute and per cent increase of spirometric results and SaO<sub>2</sub> from baseline after terbutaline treatment. The mean absolute increase of PEF and SaO<sub>2</sub> for the MDI group, and the mean per cent increase of FEV<sub>1</sub>, PEF, and SaO<sub>2</sub> were significantly higher than those for the nebuliser group. The mean absolute and per cent increase of SaO<sub>2</sub> for the nebuliser group was negative. Thirteen (23%) children in the MDI group and 26 (47%) in the nebuliser group had a decreased SaO<sub>2</sub> after treatment (p=0.0079).

### Discussion

The results of this study showed that both MDI and nebuliser treatment were effective in treating clinical severity and airway obstruction in children with acute asthma, but the MDI (with a holding chamber) method was better than the nebuliser method particularly for improvement of the SaO<sub>2</sub> and in some measurements of spirometry.

In the past, bronchodilation achieved by nebulisation was considered to be greater than that obtained by an MDI, and therefore the former was the treatment of choice for in hospital treatment of asthma.<sup>20</sup> However, recent reports have suggested that there is little difference between these two forms of treatment in asthmatic patients.<sup>8-13</sup> Although Olivenstein *et al* found significantly greater absolute increases from baseline for FEV<sub>1</sub> and FEF<sub>25-75%</sub> with the MDI compared with the ultrasonic nebuliser,<sup>21</sup> and Hodder *et al* reported superior bronchodilation in the MDI group compared with the nebulisation group,<sup>22</sup> the degree of bronchodilation achieved in

asthmatic patients was later demonstrated to be a reflection of the dose of bronchodilator administered, not of the mode of administration.<sup>12, 23</sup> The equivalent response dose of MDI to nebuliser has been reported to be between 1:1 to 1:12.5.<sup>12, 13, 23-26</sup> This wide range reflects the variability in dose delivered to the lungs by different nebulising systems. In this study design, 0.75 mg of terbutaline given by MDI was compared with 5 mg of terbutaline given by nebuliser; this is an equivalent dosage for bronchodilation, according to the recent report of Colacone *et al*.<sup>12</sup> They also used the AeroChamber for holding and compared its effects with the air compressor nebuliser. Most of the studies measured only FVC and FEV<sub>1</sub>,<sup>8-11</sup> with a few reports also measuring the dyspnoea score.<sup>12, 13</sup> In this study, more parameters (SaO<sub>2</sub>, pulse rate, FVC, FEV<sub>1</sub>, PEF, FEF<sub>25-75%</sub>, and clinical severity score) were compared and better results were found in the MDI group. Compared with the recent study by Kerem *et al*, who found spacers and nebulisers were equally effective means of delivering β<sub>2</sub> agonists to children with acute asthma,<sup>13</sup> our patients were of smaller mean age and had higher mean baseline per cent predicted FEV<sub>1</sub> and mean SaO<sub>2</sub>. A clinical diagnosis of an acute asthma attack in patients with wheezing cough was our major inclusion criteria rather than an initial FEV<sub>1</sub> between 20% and 70% of the predicted value. Moreover, we compared the MDI group with the nebuliser group 15 minutes after the beginning of treatment, not timing from the termination of treatment. Many of these factors could have an influence on the study results. While the superior bronchodilation effect of the MDI found in this study may reflect only the different doses of terbutaline administered or different timing at the evaluation after treatment, the lower SaO<sub>2</sub> found with the nebuliser compared with that of the MDI invites attention.

The causes for oxygen desaturation have been suggested by some authors to result from a change in the ventilation-perfusion ratio,<sup>27, 28</sup> and by others to be a change in pH and osmolality in response to the nebulised solutions,<sup>29-31</sup> which have been well documented to produce bronchoconstriction in asthmatic subjects.<sup>32, 33</sup> The MDI method with a valved holding chamber removes the large aerosol particles, which often deposit themselves in the mouth and throat while allowing the smaller treatment particles to pass into the lungs. This provides effective treatment and helps to reduce unwanted side effects. By increasing effective pulmonary aerosol deposition,<sup>6, 7</sup> and removing unwanted upper airway deposition, the former provided more effective bronchodilation and the latter reduced cardiovascular effect, and this could make ventilation-perfusion mismatch less likely. Moreover, MDI administration gave no problem with osmotic change during nebuliser treatment.<sup>30, 31</sup> The nebuliser group were more vulnerable to temperature drop,<sup>34</sup> acidity, and osmolality change of the nebulised solution. All these factors can decrease the bronchodilation effect of terbutaline. O'Callaghan *et al*, in their study

Table 3 Mean absolute and per cent increase of spirometric results and SaO<sub>2</sub> from baseline after terbutaline treatment; values are mean (SD)

	Mean absolute increase			Mean per cent increase		
	MDI	Nebuliser	p Value*	MDI	Nebuliser	p Value*
FVC	0.23 (0.34)	0.21 (0.23)	NS	19.9 (25.2)	16.7 (18.1)	NS
FEV <sub>1</sub>	0.23 (0.21)	0.17 (0.18)	NS	22.9 (21.0)	15.4 (16.1)	0.0391
PEF	32.6 (37.7)	10.2 (34.7)	0.0016	27.7 (38.4)	7.7 (25.1)	0.0017
FEF <sub>25-75%</sub>	0.39 (0.50)	0.22 (0.41)	NS	82.5 (298.4)	26.5 (48.3)	NS
SaO <sub>2</sub>	0.54 (1.64)	-0.47 (1.84)	0.0029	0.58 (1.72)	-0.47 (1.93)	0.0031

\*Computed by two tailed unpaired Student's *t* test.

in infants, found nebulised salbutamol induced bronchoconstriction was greatest at five minutes after nebulisation, lasting for up to 15 minutes.<sup>29</sup> Prendiville *et al* also reported that the hypoxic effect of salbutamol and the decline in forced expiratory flow rate was still present 20 minutes after nebulisation.<sup>35</sup> Therefore, our nebulised patients were probably influenced by the hypoxic effect when they were measured for  $SaO_2$ , which was usually masked by the oxygen supply in the studies using oxygen as the driving gas.<sup>8-13</sup>

The possibility that there might also be a decrease in  $SaO_2$  very soon after administration of terbutaline by MDI that was missed by our later measurements causes concern. Harris used salbutamol given by MDI, without a holding chamber, in asthmatic patients and detected the phenomenon of hypoxaemia even at 30 minutes after treatment.<sup>27</sup> Altogether 23% of our group using the MDI had their  $SaO_2$  decreased after treatment. In general, however, the decrease was less frequent and severe than that of the nebuliser group. The two methods of aerosol administration were quite different. It took less than one minute for the MDI and about 10 minutes for the nebuliser to complete the treatment. The drug effect started soon after MDI administration but did so by accumulation during the nebulisation. We made the comparison 15 minutes after the beginning (not termination) of terbutaline administration because, on the one hand, we attempted to study the difference after the two groups of patients had spent the same time in respiratory treatment room; on the other hand, in our previous study with a similar design, the  $SaO_2$  of nebulised patients significantly improved as early as two minutes after the beginning of terbutaline nebulisation.<sup>36</sup> This led us to speculate that the improvement of pulmonary function started before the end of nebulisation. We therefore made comparison timings from the beginning of treatment. However, a further study of serial  $SaO_2$  monitoring, with timing from the beginning of administration of the drug and until at least 30 minutes after the termination of treatment for both groups, is needed. Although the mean absolute decrease of  $SaO_2$  in the nebuliser group was only 0.47%, this treatment might endanger the life of high risk asthmatic patients. Therefore, oxygen should, if possible, be chosen as the driving gas in treating severe asthmatic patients by nebuliser.

In addition to having less adverse effects, MDI treatment with a valved holding chamber can be very easily performed by patients themselves, or with help from physicians or parents if the patients are too young. This is therefore a portable, convenient method to provide quick symptom relief during an acute asthmatic attack and thus prevents it progressing. Frequent visits to an emergency room may be avoided. Another advantage is that the substitution of MDI treatment for nebuliser treatment is the time and finance savings<sup>37 38</sup>; this is beneficial for health care providers and receivers, as well as for health insurance providers.

In conclusion, aerosol treatment by MDI (with a valved holding chamber) in this study is

superior to nebuliser treatment in terms of  $SaO_2$  and some spirometric measurements. In patients with severe asthma inhaled  $\beta_2$  bronchodilators should be given with caution and there should be an awareness of the possibility of oxygen desaturation, especially when room air is used as the driving gas.

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