

## ORIGINAL ARTICLE

## Two administration methods for inhaled salbutamol in intubated patients

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**Aims:** To compare serum concentrations and effects on respiratory mechanics and haemodynamics of salbutamol administered by small volume nebuliser (SVN) and metered dose inhaler (MDI) plus spacer.

**Methods:** Blinded, randomised, crossover study in 12 intubated infants and children (mean age 17.8 months) receiving inhaled salbutamol therapy. Subjects received salbutamol as 0.15 mg/kg by SVN and four puffs (400 µg) by MDI plus spacer at a four hour interval in random order. Passive respiratory mechanics were measured by a single breath/single occlusion technique, and serum salbutamol concentrations by liquid chromatography–mass spectrometry at 30 minutes, 1, 2, and 4 hours after each dose. Haemodynamics (heart rate and blood pressure) were recorded at each measurement time.

**Results:** There was no difference in percentage change in respiratory mechanics or haemodynamics between the two methods of administration. Mean area under the curve (AUC<sub>0–4</sub>) was 5.86 for MDI plus spacer versus 4.93 ng/ml × h for SVN.

**Conclusions:** Serum concentrations and effects on respiratory mechanics and haemodynamics of salbutamol were comparable with the two administration methods under the conditions studied. Future studies are needed to determine the most effective and safe combination of dose and administration method of inhaled salbutamol in mechanically ventilated infants and children.

Nebulised  $\beta_2$  agonists are commonly used in mechanically ventilated infants and children<sup>1–3</sup> despite reported disadvantages with this administration method. Nebulisation is expensive,<sup>4</sup> provides a possible source for contamination,<sup>5</sup> and requires adjustment of tidal volume and inspiratory flow during administration.<sup>6</sup> There is also variability in the output of different brands and different lots of the same brand.<sup>7</sup> In contrast, administration by metered dose inhaler (MDI) is easier, faster, and provides more consistent drug delivery.<sup>6</sup>

In comparisons of the two administration methods enrolling mechanically ventilated adults, advantages such as greater lung deposition<sup>8</sup> and cost savings<sup>9</sup> were documented with MDI. Despite the advantages in intubated adults and the extensive use in ambulatory children, only one comparison between the two administration methods has been completed in ventilator dependent infants or children. In intubated infants with bronchiolitis, albuterol administered by MDI was as efficacious as nebulised albuterol as determined by improved respiratory mechanics.<sup>10</sup> However, no mechanism was used to compare lung deposition in these patients. It has been suggested that because there is no oropharyngeal deposition, and therefore no enteral absorption, serum concentrations of an inhaled drug may best represent lung deposition in intubated patients.<sup>11</sup>

The primary objectives of this investigation were to compare the serum concentrations and effect on respiratory mechanics of salbutamol administered by small volume nebuliser (SVN) and MDI plus spacer in mechanically ventilated children. Effects on haemodynamics and administration times with each method were also compared.

## METHODS

The Institutional Review Board for Human Research at the Medical University of South Carolina approved this protocol. Written informed consent was obtained from the subject's parent or legal guardian. Mechanically ventilated infants and children between 1 month and 12 years with an indwelling

intravenous or arterial catheter who were receiving salbutamol therapy in the paediatric intensive care unit were eligible for study screening. Patients requiring salbutamol more frequently than every four hours, with cardiac dysrhythmias, or hypersensitivity to salbutamol were excluded.

Screening involved documenting reversibility of airway obstruction with salbutamol as defined by a  $\geq 15\%$  improvement in respiratory system compliance (Crs) or respiratory system resistance (Rrs) from baseline. Specifically, baseline Crs and Rrs were measured four hours after the subject's last dose of salbutamol. The subject's salbutamol regimen as ordered by the clinical team was then administered, with Crs and Rrs measurements repeated 30 minutes after salbutamol administration.

Passive respiratory mechanics were measured by a single breath/single occlusion technique<sup>12</sup> with a computerised infant pulmonary function device (2600, SensorMedics, Yorba Linda, California).<sup>13</sup> Calculations for Crs and Rrs were compiled from 3–13 sequential flow/volume curves. Curves were considered acceptable for analysis if the airway pressure reached a plateau and the flow/volume relation was linear.<sup>14</sup>

If an improvement in Crs or Rrs with salbutamol was shown, the crossover portion of the protocol was started after a four hour washout. At baseline, excess respiratory secretions were removed by endotracheal suctioning. Fifteen to 30 minutes after suctioning, baseline haemodynamics were recorded and respiratory mechanics measured as described above. A baseline salbutamol serum sample was also obtained. In a blinded, randomised, crossover design, each subject received salbutamol sulphate by SVN and salbutamol by MDI plus spacer. The order of administration was determined by a computer generated randomisation table.

**Abbreviations:** AUC<sub>0–4</sub>, area under the serum concentration–time curve from 0 to 4 hours; Crs, respiratory system compliance; DBP, diastolic blood pressure; ETT, endotracheal tube; HR, heart rate; MDI, metered dose inhaler; Rrs, respiratory system resistance; SBP, systolic blood pressure; SVN, small volume nebuliser

**Table 1** Patient demographics

Pt	Age (mth)	Weight (kg)	Diagnosis
1	42.0	16.0	Status asthmaticus
2	1.0	4.1	Apnoea/respiratory failure
3	1.8	3.2	Respiratory failure
4	26.1	10.7	BPD/RSV
5	1.6	3.2	RSV
6	10.0	11.1	Pneumonia
7	3.0	2.7	RSV
8	120.0	37.5	ARDS
9	1.6	4.0	Respiratory failure
10	1.1	3.7	RSV
11	2.4	5.2	RSV
12	2.6	2.6	BPD/RSV
Mean	17.8	8.6	
(SD)	(34.6)	(10.1)	

BPD, bronchopulmonary dysplasia; RSV, bronchiolitis due to respiratory syncytial virus; ARDS, acute respiratory distress syndrome.

The SVN treatment arm involved the administration of 0.15 mg/kg<sup>1.2</sup> (maximum 5 mg)<sup>15</sup> of 0.5% salbutamol sulphate solution (Ventolin, Glaxo Wellcome, Research Triangle Park, North Carolina) diluted to 4 ml with 0.9% saline and administered by a SVN from one lot (T Up-Draft II Neb-U-Mist, Hudson Respiratory Care, Inc., TemelUCA, California). For infants <7 kg, the nebuliser was attached to a 12.75 cm reservoir of respiratory circuit tubing (total volume 10 ml). It was placed in the inspiratory limb of an infant ventilator circuit (Airlife Isothermal infant circuit, Allegiance Healthcare Corporation, McGaw Park, Illinois) at the end of the temperature probe (20 cm from the connection to the endotracheal tube (ETT)). The SVN with the tee piece was attached to a 14.5 cm reservoir of respiratory circuit tubing (total volume 50 ml) for children 7–30 kg. It was placed between a paediatric ventilator circuit (Airlife Isothermal paediatric circuit, Allegiance Healthcare Corporation) and an elbow adapter attached to the endotracheal tube. For children >30 kg, the latter setup was used with an adult ventilator circuit (Airlife Isothermal adult circuit, Allegiance Healthcare Corporation). All subjects received warm, humidified gas mixtures. The dose was administered by 6-LPM flow with adjustments made to the inspiratory flow and tidal volume so total flow and tidal volume remained unchanged during salbutamol administration. Otherwise, ventilator modes and settings were determined by the clinical team and were not altered by participation in the study. Administration by SVN was considered complete when sputtering stopped and no more aerosol was produced.<sup>6</sup>

The MDI treatment arm consisted of four puffs (100 µg/puff without the commercially available mouthpiece) of salbutamol (Ventolin, Glaxo Wellcome) based on previous *in vitro* data.<sup>16, 17</sup> The MDI canister was vigorously shaken and inserted in an inverted position into a spacer (AeroChamber MV-15, Monaghan Medical, Plattsburgh, New York) which was placed between the ventilator circuit and elbow adapter attached to the endotracheal tube. The canister was actuated at end expiration with actuations separated by one minute. The spacer was left in place for one minute after the fourth actuation.

After the dose of salbutamol, respiratory mechanics were measured as described above by a respiratory therapist blinded to the order of treatments at 30 minutes, 1, 2, and 4 hours after the beginning of drug administration. Vital signs (heart rate (HR), systolic and diastolic blood pressure (SBP, DBP), respiratory rate, oxygen saturation, and temperature) were continuously monitored throughout the study. Heart rate and blood pressure measurements by electrocardiographic signals and an indwelling arterial catheter, respectively, were recorded at each of the measurement times. Before and at 15 minutes from the beginning of drug administration, vital signs excluding temperature were also recorded. Serum samples (2 ml whole blood) for the determination of salbutamol concentrations were obtained at 30 minutes, 1, 2, and 4 hours after the beginning of drug administration in subjects >10 kg, with the 30 minute sample excluded in subjects <10 kg. Each subject was crossed over to the alternate administration method four hours after the first dose and measurements were repeated. The time required to administer salbutamol was recorded for each administration method.

**Table 2** Mechanical ventilation parameters and baseline pulmonary mechanics

Pt	VT	f	FiO <sub>2</sub>	I time	PS	ETT	Cr <sub>s</sub>	Cr <sub>s</sub> /kg	R <sub>rs</sub>
1	200	12	0.60	0.90	10	5.0	11.90	0.74	0.085
2	70	18	0.30	0.60	15	3.5	1.20	0.29	0.141
3	65	25	0.35	1.25	20	3.5	2.23	0.67	0.132
4	180	15	0.60	0.60		4.5	8.26	0.77	0.057
5	50	28	0.35	0.65	15	3.5	1.35	0.42	0.374
6	150	12	0.45	0.90	15	4.5	5.60	0.51	0.053
7	35	18	0.40	0.60	10	3.5	1.29	0.50	0.093
8	320	26	0.55	0.50		6.0	7.99	0.21	0.035
9	70	20	0.45	0.80	15	3.5	1.46	0.36	0.185
10	50	28	0.50	0.75	10	3.5	1.41	0.52	0.083
11	75	20	0.40	0.90	10	4.0	2.96	0.57	0.750
12	50	10	0.35	0.65	10	3.0	1.99	0.77	0.098
Mean							3.97	0.53	0.174
(SD)							(3.60)	(0.19)	(0.202)

VT, tidal volume (ml); f, frequency (breaths/min); FiO<sub>2</sub>, fraction of inspired oxygen (%); I time, inspiratory time (sec); PS, pressure support (cm H<sub>2</sub>O); ETT, endotracheal tube size (mm); Cr<sub>s</sub>, respiratory system compliance (ml/cm H<sub>2</sub>O); Cr<sub>s</sub>/kg, respiratory system compliance/kg (ml/cm H<sub>2</sub>O/kg); R<sub>rs</sub>, resistance (cm H<sub>2</sub>O/ml/sec).

**Table 3** Difference in percentage change in respiratory mechanics with MDI versus SVN

Time (h)	CrS (SEM)	p	Rrs (SEM)	p
0.5	6.6 (7.8)	0.67	-6.5 (7.5)	0.33
1	11.3 (10.1)	0.52	-0.6 (10.4)	0.95
2	-7.0 (10.5)	0.58	-7.1 (17.9)	0.64
4	-18.6 (14.2)	0.18	-16.0 (19.6)	0.48

Statistically significant ( $p < 0.05$ ) differences in percentage changes in respiratory mechanics with MDI versus SVN at each sample time determined by Wilcoxon signed rank test. Values represent means (SEM). Crs, respiratory system compliance (ml/cm H<sub>2</sub>O); Rrs, respiratory system resistance (cm H<sub>2</sub>O/ml/sec); MDI, metered dose inhaler plus spacer; SVN, small volume nebuliser.

Serum salbutamol concentrations were measured with liquid chromatography–mass spectrometry by Glaxo Wellcome as reported previously.<sup>18</sup> Standard curves were generated using calibration standards at 0.1, 2, 4, 8, 16, 25, and 50 ng/ml salbutamol. For all standard concentrations, the inter- and intra-assay precision (%CV) and the bias were all less than 15% over the limits of quantification.

Elimination rate constants were calculated by analysing serum salbutamol concentration versus time curves using a weighted non-linear regression program (ADAPT).<sup>19</sup> Residuals were weighted as inverse variance of the assay. Trapezoidal integration was used to calculate the area under the serum concentration–time curve from 0 to 4 hours ( $AUC_{0-4}$ ). Because subjects enrolled were receiving salbutamol therapy prior to enrolment, corrections for residual salbutamol concentrations prior to each dose were made. Using the elimination rate constant, the fraction of baseline concentration remaining at each sample time was calculated and subtracted from each measured salbutamol sample to provide an adjusted concentration.

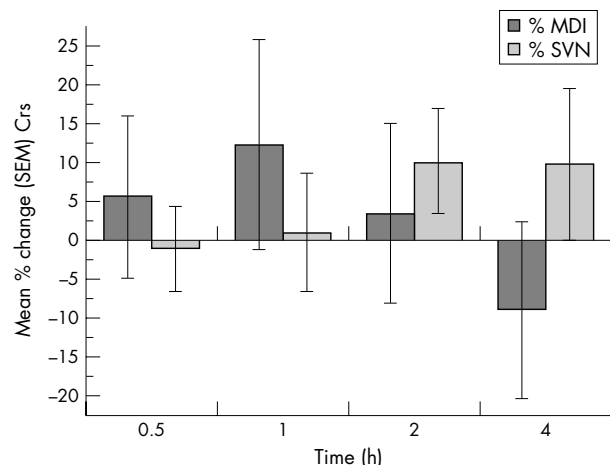
A Wilcoxon signed rank test was used to compare differences in the percentage change in respiratory mechanics (CrS and Rrs) between the SVN and MDI plus spacer at each sample time. A paired *t* test was used to compare differences in the mean percentage change in haemodynamics (HR, SBP, and DPB) between the two methods at each sample time. Correlation coefficients were calculated to determine significant relations between the following: (1) mean adjusted salbutamol concentrations and mean percentage change in respiratory mechanics or haemodynamics for all subjects at each sample time; and (2) subject age and elimination rate constant. A paired *t* test was used to compare the respiratory mechanics and haemodynamics prior to each treatment, percentage changes in vital signs 15 minutes after salbutamol administration, and the pharmacokinetic parameters (elimination rate

constant and  $AUC_{0-4}$ ) for the two methods. A two tailed Student's *t* test was used to compare administration times for each method. Statistical significance was defined as  $p < 0.05$ . All data are reported as mean (SD) unless specified otherwise.

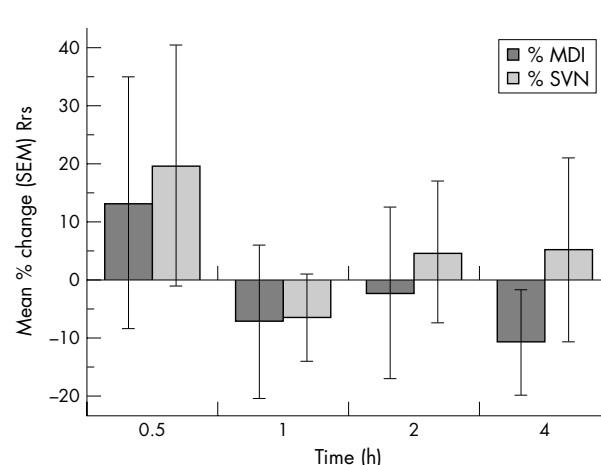
## RESULTS

Twelve mechanically ventilated infants and children aged 17.8 (34.6) months (range 1–120 months) were enrolled. Table 1 lists subject demographics and table 2 the mechanical ventilator parameters and respiratory mechanics prior to the first study dose. All subjects received mechanical ventilation with a volume cycled infant/paediatric ventilator (VIP Bird, Bird Products Corp., Palm Springs, California), with the exception of one subject (subject 8) who received ventilation with a volume cycled ventilator commonly used for older children and adults (Veolar, Hamilton Medical, Inc., Reno, Nevada). All subjects were sedated with midazolam ( $n = 8$ ) or fentanyl ( $n = 3$ ) infusions, intermittent intravenous midazolam ( $n = 2$ ) or lorazepam ( $n = 1$ ) as needed, and/or chloral hydrate as needed ( $n = 10$ ). Five subjects were paralysed with a vecuronium infusion. Subjects were concurrently treated with corticosteroids ( $n = 3$ ), theophylline ( $n = 2$ ), or cromolyn ( $n = 1$ ), but no other inhaled bronchodilators were administered throughout the study. No changes in concomitant medication were made during the two crossover periods.

To qualify for protocol enrolment, one subject showed a  $\geq 15\%$  increase in Crs, eight showed a  $\geq 15\%$  reduction in Rrs, and three had both findings. All 12 subjects showed a response to salbutamol during the crossover portion of the protocol by a  $\geq 15\%$  improvement in Crs or Rrs by either method at one or more measurement times. There were nine responders to each administration method. Improved Crs was shown in seven subjects by SVN administration and four subjects by MDI plus spacer administration. Eight subjects in each group showed decreased Rrs. There was no difference between the two



**Figure 1** Percentage change from baseline for Crs for SVN and MDI plus spacer.



**Figure 2** Percentage change from baseline for Rrs for SVN and MDI plus spacer.

**Table 4** Difference in percentage change in haemodynamics during crossover with MDI versus SVN

Time (h)	HR	p	SBP	p	DBP	p
0.5	-3.3 (5.6)	0.59	8.4 (11.8)	0.53	5.5 (11.0)	0.64
1	3.1 (2.8)	0.32	-2.2 (10.3)	0.84	-4.8 (12.9)	0.72
2	10.1 (5.7)	0.13	-4.5 (8.2)	0.60	-0.9 (9.5)	0.93
4	6.5 (8.5)	0.47	9.9 (16.6)	0.58	12.5 (20.4)	0.56

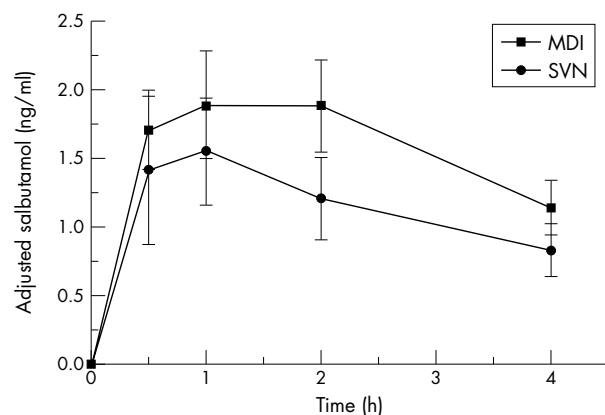
Statistically significant ( $p < 0.05$ ) percentage changes in haemodynamics with each method of administration at each sample time determined by paired *t* test. Values represent means (SEM).

HR, heart rate (beats per minute); SBP, systolic blood pressure (mm Hg); DBP, diastolic blood pressure (mm Hg); MDI, metered dose inhaler plus spacer; SVN, small volume nebuliser.

methods in percentage change in Crs or Rrs at any sample time (table 3). Figures 1 and 2 show the changes in respiratory mechanics. Subjects were able to serve as their own control as there were no significant differences in respiratory mechanics prior to the first and second method of administration (Crs: 3.84 (3.30) versus 4.02 (3.80) ml/cm H<sub>2</sub>O,  $p = 0.63$ ; and Rrs: 0.16 (0.20) versus 0.15 (0.16) ml H<sub>2</sub>O/ml/s,  $p = 0.64$ ).

During salbutamol dosing, the mean percentage changes in vital signs 15 minutes after administration with SVN and MDI plus spacer were: HR: 1.89 (2.92)% versus 2.84 (2.72)% ( $p = 0.63$ ); SBP: 0.37 (5.16)% versus 1.33 (3.71)% ( $p = 0.77$ ); DBP: -2.67 (19.90)% versus -1.1 (3.58)% ( $p = 0.91$ ); respiratory rate: 24.86 (44.0)% versus 19.98 (68.74)% ( $p = 0.78$ ); and O<sub>2</sub> saturation: -0.84 (4.37)% versus -0.21 (3.41)% ( $p = 0.79$ ). There was also no difference between the two methods in percentage change in haemodynamics (HR, SBP, or DBP) at any sample time during the crossover portion of the protocol (see table 4).

The AUC<sub>0-4</sub> values for each administration method were not significantly different (fig 3). There were no significant associations between mean adjusted salbutamol concentrations with SVN and MDI plus spacer combined and percentage change in Crs ( $r = 0.59$ ,  $p = 0.41$ ), Rrs ( $r = 0.14$ ,  $p = 0.86$ ), or haemodynamics (HR:  $r = 0.12$ ,  $p = 0.88$ ; SBP:  $r = 0.91$ ,  $p = 0.09$ ; DBP:  $r = 0.65$ ,  $p = 0.35$ ). Elimination rate constants for salbutamol administered by SVN and MDI plus spacer were 0.18 (0.06) h<sup>-1</sup> and 0.20 (0.07) h<sup>-1</sup> ( $p = 0.47$ ), with half lives of 4.36 (1.56) and 3.71 (1.07) h ( $p = 0.4$ ), respectively. Elimination rate constant or half life was not significantly associated with age (MDI:  $r = 0.11$ ,  $p = 0.79$  and  $r = 0.03$ ,  $p = 0.94$ ; SVN:  $r = 0.01$ ,  $p = 0.98$  and  $r = 0$ ,  $p = 0.99$ , respectively). The administration time for SVN was significantly longer at 13.1 (2.8) versus 5.2 (1.7) minutes for MDI plus spacer ( $p < 0.001$ ).



**Figure 3** Mean (SEM) adjusted salbutamol concentrations over the dosing interval for SVN and MDI plus spacer. Mean (SD) AUC<sub>0-4</sub> of 5.86 (3.11) for MDI plus spacer versus 4.93 (2.67) ng/mL × h for SVN ( $p = 0.45$ , paired *t* test).

## DISCUSSION

This investigation showed an improvement in respiratory mechanics (Crs and/or Rrs) in all 12 subjects with no significant difference between the two methods used for salbutamol administration. This finding agrees with a prior blinded, crossover comparison of SVN and MDI that enrolled intubated infants with bronchiolitis. An improvement in Crs and Rrs for up to two hours was found with no difference in the degree of improvement between the two methods.<sup>10</sup> The finding of improved Crs in this and other studies<sup>10–20–22</sup> has been speculated to be caused by bronchodilatation of the small peripheral airways leading to recruitment of air spaces and an increased lung volume.<sup>20–22</sup> A crossover comparison enrolling ventilator dependent adults also reported similar improvements in passive expiratory flow for both MDI and SVN administration.<sup>9</sup>

It should be noted that lung deposition in ventilator supported patients is highly affected by the specific administration equipment and technique used, including brand of SVN<sup>7–23</sup> or MDI actuator device,<sup>16–24–26</sup> position within the ventilator circuit,<sup>27</sup> synchronisation of MDI actuation with breaths,<sup>25</sup> allowing time between actuations,<sup>28</sup> and volume fill of the SVN.<sup>23–27</sup> Characteristics of the ventilator circuit may also be significant, including humidity<sup>16–17–23</sup> and density<sup>29–30</sup> of the inhaled gas, ETT size,<sup>31</sup> and ventilator mode<sup>32</sup> and settings.<sup>23</sup> In addition to lung deposition, therapeutic response may be influenced by a patient's airway anatomy and disease severity.<sup>6</sup> There also continues to be a controversy concerning the efficacy of bronchodilators in infants.<sup>33</sup> As this was a crossover study, differences in the ventilator circuit and patient related factors were negated leaving the administration equipment and technique as primary issues. As seemingly subtle changes can significantly change lung deposition, our results are dependent on the conditions studied.

Despite the threefold larger dose administered by SVN in this study, there was no difference in AUC<sub>0-4</sub> between the two methods. Assuming that serum concentrations of salbutamol indirectly reflect systemic absorption of drug deposited in the respiratory tract of intubated patients,<sup>11</sup> this finding supports prior reports of greater lung deposition of  $\beta$  agonists with MDI versus SVN ( $5.65 \pm 1.09\%$  versus  $1.22 \pm 0.35\%$ , respectively).<sup>8</sup>

The doses of salbutamol used in this study improved respiratory mechanics in the subjects enrolled. In this population, weight based dosing is typically recommended for SVN,<sup>1</sup> while investigations of MDI administration in mechanically ventilated paediatric models suggest that the relatively reduced percentage drug delivery through smaller ETT preclude the need for weight based dosing.<sup>16–17</sup> Four puffs administered by MDI with the Airlife MediSpacer with manual ventilation was also reported as safe and effective in a prior paediatric investigation.<sup>10</sup> In a dose-response study enrolling mechanically ventilated adults with chronic obstructive pulmonary disease, four puffs offered the best combination of bronchodilator effect and safety.<sup>34</sup> To our knowledge, no dose-response study is available in ventilator dependent infants and children. Therefore, it is possible that higher doses by either administration method would safely produce greater improvements in respiratory mechanics.

Intrasubject<sup>35</sup> and intersubject<sup>36</sup> variability in respiratory mechanics is a limitation of this and other studies in paediatric populations. In healthy term neonates during the first three days of life, mean (SD) intrasubject coefficients of variation were reported as 14 (7)% (range 3–28%) for specific dynamic compliance and 28 (14)% (range 11–69%) for resistance. These investigators recommended that the upper 95% confidence limit of variability be defined as a significant change after a therapeutic intervention.<sup>35</sup> The intrasubject coefficients of variation in this investigation were 8.6 (6.1)% for Crs and 13.8 (9.2)% for Rrs. Therefore, the upper 95% confidence interval for the respiratory mechanics parameters would be 12% and 19%, respectively. If these values were used to define response, the results for Crs would not change. For Rrs, there would be seven instead of eight subjects who showed an improvement with administration by SVN. Instead of nine responders, there would be eight for each method. All 12 patients would still have responded by an improvement in one of the parameters of respiratory mechanics.

Consistent with the findings for respiratory mechanics, changes in haemodynamics during the dosing interval and vital signs during drug administration were not different for the two administration methods. However, the small number of subjects enrolled in this investigation with the potential for tolerance to systemic effects caused by prior salbutamol exposure does not allow for adequate evaluation of these side effects.

This investigation showed MDI plus spacer to be the more efficient method with regard to administration time. These findings agree with those reported in ventilator dependent adults in which significantly less time was required to administer albuterol by MDI versus SVN (5.8 versus 15.5 minutes, respectively).<sup>9</sup> The cost savings associated with MDI administration have been previously documented.<sup>4, 9, 10</sup>

## Conclusions

Serum concentrations and effects on respiratory mechanics and haemodynamics of salbutamol administered by MDI plus spacer and SVN in intubated children were comparable under the conditions studied. Future investigations are needed to determine the most effective and safe combination of dose and administration method of inhaled salbutamol in mechanically ventilated infants and children.

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