Randomized comparison of two spacer devices in subjects with reversible airflow limitation

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OBJECTIVE: To assess a new spacer device, the ACE, by comparing it with the Aerochamber in subjects with reversible airflow limitation and assessing the change in lung function after inhaled bronchodilator.
DESIGN: A randomized single-blind cross-over trial was performed.
SETTING: Hospital-based pulmonary function laboratory.
POPULATION STUDIED: Thirty subjects with reversible airflow limitation. Mean forced expired volume in 1 s (FEV_1) was 1.37 L, range 0.8 to 3.3 L. All subjects had previously shown at least 15% reversibility after inhaled bronchodilator. All inhaled bronchodilators were witheld for 6 h. Subjects were studied on two separate days. Four subjects were excluded from the final analysis because baseline FEV_1 varied by greater than 10% between the two study days. Maximum expiratory flow rates were used as the primary outcome measure. Change in heart rate was assessed for adverse effects.
INTERVENTIONS: The change in maximum expiratory flow rates was assessed 15 mins after two, three and four puffs of inhaled salbutamol delivered via one of the spacer devices. The use of spacer was randomized.
RESULTS: Data from 26 subjects were analyzed. Baseline FEV_1 was similar on the two study days: 1.37±0.13 L (ACE) and 1.38±0.14 L (Aerochamber). The change in FEV_1 was similar on both study days. The change in all the maximum expiratory flow rates was similar with both spacer devices. FEV_1 after four puffs of salbutamol was 1.72±0.16 L (ACE) and 1.71±0.16 L (Aerochamber).
CONCLUSION: The bronchodilation achieved was similar with both spacers. Because the ACE is cheaper, it may offer cost savings to individuals or institutions.

Key Words: *Asthma, Bronchodilators, Chronic obstructive pulmonary disease, Spacer devices*

Comparaison randomisée de deux dispositifs d'espacement chez des sujets présentant une limitation réversible du débit aérien

OBJECTIF : Évaluer un nouveau dispositif d'espacement, l'ACE, en le comparant à l'Aérochambre chez des sujets présentant une limitation réversible du débit aérien, et estimer la variabilité de la fonction pulmonaire après l'inhalation d'un bronchodilatateur.
MODÈLE : Essai randomisé croisé à simple insu.
CONTEXTE : Laboratoire de fonction pulmonaire d'un hôpital.
POPULATION ÉTUDIÉE : Trente sujets présentant une limitation réversible du débit aérien. Le volume expiratoire maximum seconde (VEMS) moyen était de 1,37 L, écart:0,8–3,3 L. Tous les sujets avaient antérieurement démontré une réversibilité d'au moins 15 % après l'inhalation d'un bronchodilatateur. L'administration des bronchodilatateurs par inhalation a été suspendue pendant 6 heures. Les patients ont été étudiés au cours de deux jours distincts. Quatre sujets ont été exclus de l'analyse finale car leur VEMS de base avait varié de plus de 10 % entre les deux jours d'étude. Les débits expiratoires de pointe (DEP) ont été retenus comme principale mesure objective. On a mesuré les variations du rythme cardiaque pour déceler les effets indésirables.
INTERVENTIONS : La variabilité des DEP a été évaluée 15 mn après la prise de deux, trois et quatre bouffées de salbutamol en inhalation administrées à l'aide d'un des deux dispositifs d'espacement. L'utilisation du dispositif d'espacement était randomisée.
RÉSULTATS : Les données recueillies sur 26 sujets ont été analysées. Le VEMS de base était identique pendant les deux jours d'étude: 1,37±0,13 L (ACE) et 1,38±0,14 L (Aérochambre). La variabilité du VEMS était similaire pendant les deux jours d'étude. Tous les DEP présentaient la même variabilité quel que soit le dispositif d'espacement utilisé. Le VEMS après quatre bouffées de salbutamol était de 1,72±0,16 L (ACE) et de 1,71±0,16 L (Aérochambre).
CONCLUSION : La bronchodilatation obtenue à l'aide des deux dispositifs d'espacement était identique. Moins coûteux, l'ACE peut représenter une source d'épargne pour les individus et les institutions.

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THE METERED DOSE INHALER (MDI) IS THE DEVICE MOST commonly used to deliver drugs to the lung in patients with obstructive lung diseases. In many countries the MDI is used even in emergency situations as it has been shown that they are as effective as nebulizers but cost less (1-3). However, to obtain the optimum effect from the inhaled drug the patient must master the technique needed to actuate the MDI and coordinate that action with inspiration. Several studies have shown that this is difficult for many patients (4-6) and spacer devices have been developed to simplify the technique (7-9).

In addition to improving delivery of the drug to the lung, spacer devices reduce oropharyngeal deposition of the inhaled medication, even in subjects who use the MDI in an optimal manner (10-12). Not only does this play a part in decreasing oropharyngeal adverse effects but it is particularly important now that it is recognized that inhaled steroids have the potential to produce systemic side effects (13-15). In order to minimize this potential for unwanted effects it is standard practice to recommend that all patients taking high dose inhaled corticosteroids use a spacer device.

Most patients have to pay for their own spacer device and for many this cost is prohibitive. We have evaluated a new spacer, the ACE (Diemolding Healthcare Division, New York) which is approximately half the price of other spacers. We used a randomized, single-blind, cross-over design to compare the ACE with the Aerochamber (Trudell Medical) and assessed the change in lung function achieved after inhaled bronchodilator as the outcome measure.

METHODS

Thirty subjects with reversible airflow limitation were studied. All had shown at least 15% improvement in mean forced expired volume in 1 s (FEV_1) in the three months before the study. All subjects were on inhaled corticosteroids and had been stable for at least one month before the study. Subjects were studied on two separate days in one week and at the same time of day.

On each study day the subject withheld all inhaled bronchodilators for at least 6 h. Baseline flow:volume curve was obtained (Sensormedics PFT Horizon System 5). The best flow:volume curve was selected by American Thoracic Society standards (16) from at least three attempts, and FEV_1 and maximum expiratory flow at 50% ($\dot{V}50$) and 25% ($\dot{V}25$) of vital capacity were obtained. Baseline heart rate was measured.

Two puffs of inhaled bronchodilator (salbutamol) were then delivered using one of the spacer devices and 15 mins later measurements of flow and heart rate were repeated.

After a third puff and a 15 min wait, and then a fourth puff and another 15 min wait, measurements were again made. On the second day the other spacer device was used. The order of use of spacer device was randomized.

The inhalation technique with each spacer device was the same. Subjects were blindfolded and the technologist delivered the inhaled medication. The spacer device was placed in the subject's mouth and the subject was asked to seal the lips tightly. When the subject, breathing quietly, was at end expiratory lung volume the technologist actuated the MDI and then asked the subject to inspire slowly to maximum inflation, and hold their breath for 10 s. A second puff was administered 30 s later in the same manner. Third and fourth puffs were delivered individually.

The inspiratory flow rate was controlled only by the whistling apparatus at the distal end of both devices. All the subjects had used the Aerochamber before the study and were familiar with the requirement to keep inspiratory flow rates low enough so as not to activate the whistle.

All subjects gave informed consent and the study was approved by the Hospital Research Advisory Committee.

Data from subjects were discarded if the baseline FEV_1 on the two study days differed by more than 10%. Student paired *t* test was used to analyze differences in FEV_1, $\dot{V}50$, $\dot{V}25$ and heart rate after two, three and four puffs of inhaled bronchodilator.

RESULTS

Eighteen men and 12 women (mean [± SD] age 63±16, range 20 to 79 years) were studied. The mean FEV_1 at baseline was 1.38±0.66 L (range 0.8 to 3.3). Data from four subjects had to be discarded because there was greater than 10% difference in baseline FEV_1 on the two study days.

TABLE 1
Baseline lung function and changes after inhaled bronchodilator

	FEV_1		$\dot{V}50$		$\dot{V}25$	
	ACE	Aerochamber	ACE	Aerochamber	ACE	Aerochamber
Baseline	1.37±0.13	1.38±0.14	0.78±0.15	0.85±0.16	0.31±0.23	0.32±0.28
	Not significant		Not significant		Not significant	
Two puffs	1.62±0.16	1.64±0.16	1.03±0.22	1.10±0.24	0.38±0.43	0.40±0.5
	Not significant		Not significant		Not significant	
Three puffs	1.68±0.16	1.69±0.16	1.10±0.27	1.15±0.27	0.39±0.48	0.41±0.51
	Not significant		Not significant		Not significant	
Four puffs	1.72±0.16	1.71±0.16	1.16±0.26	1.16±0.26	0.41±0.5	0.42±0.56
	Not significant		Not significant		Not significant	

Values are mean ± standard error of the mean. FEV_1 Forced expiratory volume in 1 s; $\dot{V}50$ Maximum expiratory flow at 50% of vital capacity; $\dot{V}25$ Maximum expiratory flow at 25% of vital capacity

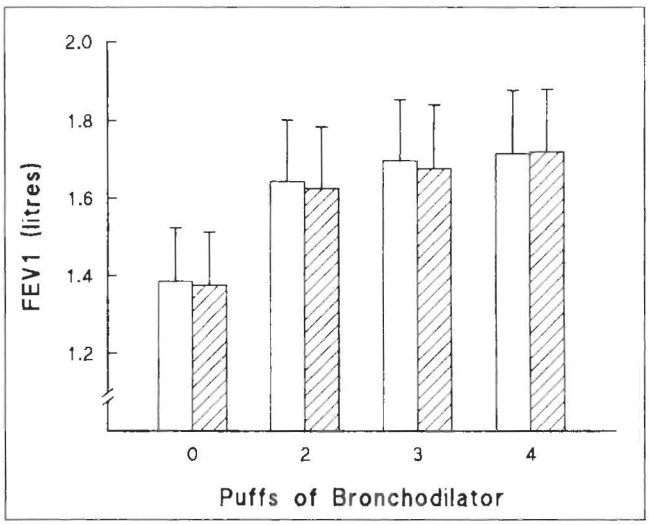

Figure 1) *Forced expired volume in 1 s (FEV_1) before and after two, three and four puffs of inhaled bronchodilator. Open bars – with Aerochamber; Hatched bars – with ACE. Values are means plus standard error*

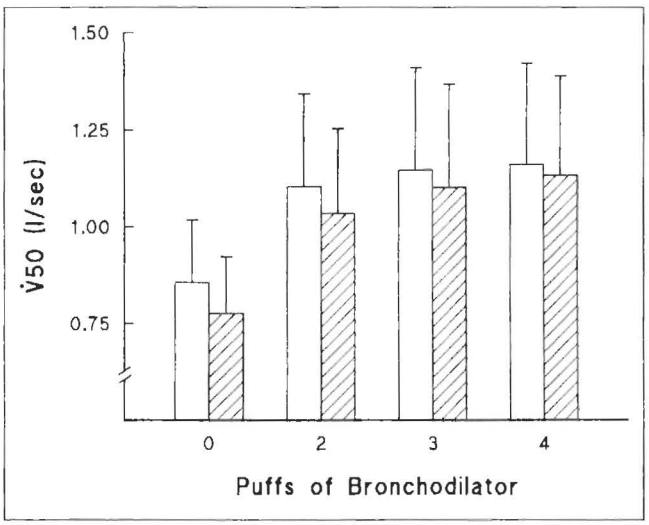

Figure 2) *Maximum expiratory flow at 50% of vital capacity ($\dot{V}50$) before and after two, three and four puffs of inhaled bronchodilator. Open bars – with Aerochamber; Hatched bars – with ACE. Values are means plus standard error*

Excluding these data did not affect the results of statistical analysis. Data from 26 subjects were therefore used for the final analysis.

In all subjects on both study days there was a significant increase in FEV_1 ($P<0.001$) after inhaled bronchodilator. There was no difference in the increase in FEV_1 on the two study days ($P>0.25$, Table 1, Figure 1). There was also no difference in the change in $\dot{V}50$ or $\dot{V}25$ after inhaled bronchodilator with either spacer device ($P>0.25$, Table 1, Figure 2).

There was no change in heart rate even after four puffs of bronchodilator with either spacer device. With the ACE heart rate was 81.5±11.8 beats/min at baseline and 79.2±10.7 beats/min after bronchodilator. Using the Aerochamber the values were 83.0±12.7 and 82.3 ±13.1 beats/min, respectively.

DISCUSSION

This study has shown that in patients with reversible airflow limitation inhaled bronchodilator delivered with a new spacer device, the ACE, results in increases in flow rates that are equivalent to those achieved when using the Aerochamber, probably the standard spacer device in general use in Canada. With either spacer device, even after four puffs of inhaled bronchodilator, there was no increase in heart rate. This indicates that the ACE delivers adequate amounts of drug to the lung without a tendency to increase adverse effects.

We chose to compare the ACE with the Aerochamber in part because the Aerochamber is the most commonly used device, but also because the size of the spacers is similar. The volume of the ACE is 170 mL while that of the Aerochamber is 145 mL. There is no clinical advantage to using larger spacers (17,18).

The ACE and the Aerochamber are structurally different and yet share some similarities. They both have one-way inspiratory valves at the proximal end and whistling adaptors at the distal end. The ACE, however, has an entrainment hole proximal to the valve. We did not find that this entrainment hole affected the bronchodilation that was achieved even at very low inspiratory flow rates in some of our subjects whose FEV_1 was less than 1 L.

With the ACE the MDI canister itself is placed in the adaptive opening at the proximal end of the device in front of the inspiratory valve. With the Aerochamber not only the canister but the whole of the MDI is inserted into the rubber cap at the distal end of the device. The Aerochamber is therefore available for use with all MDIs whereas the ACE will only be applicable for canisters that fit the adaptive opening.

This study was single-blind with an eye mask preventing the subject from knowing which spacer device was used; the drug was delivered by the technologist. We used this method because we were testing the spacer device, not the ability of the subject to use an MDI and spacer.

As the study could not be double-blind we were concerned about the possibility of technologist bias in determining which of the three flow volume curves obtained should be used for measurements. Bias was avoided by using American Thoracic Society standards to choose the best flow volume curve from which flow measurements were obtained (16).

We used changes in airway calibre assessed by FEV_1 and $\dot{V}50$ as the outcome measure because they reflect the potential clinical and symptomatic benefit to the patient with airflow limitation.

Although changes in lung function were similar whichever spacer device was used we cannot say that drug delivery to the lung was necessarily the same with both. However, rather than assess pulmonary deposition in this study, we chose to use the clinically relevant outcome measures of lung function changes.

The study sample size is larger than has been used in most previous assessments of spacer devices, but the possibility of

a type II error exists. However, the differences in bronchodilation between the two spacer devices was negligible and even if a type II statistical error were to exist, it is unlikely to be clinically relevant.

Spacer devices are now commonly recommended when an MDI is prescribed to improve drug delivery to the lung, reduce oropharyngeal side effects, and minimize the total dose of drug delivered – an important factor when high dose inhaled corticosteroids are used. They are particularly useful in the elderly and in children.

The ACE, a new spacer device, in combination with salbutamol delivered from an MDI, resulted in bronchodilation as good as that achieved with the present standard spacer, the Aerochamber. At present the cost of the ACE is less than that of the Aerochamber* and thus savings can accrue, without loss of benefit, to patients or to hospitals using spacer devices for clinical purposes. The use of either spacer device, however, does not negate the need to teach patients the optimal technique for inhalational therapy.

**At present the approximate cost to a patient of the Aerochamber, in a pharmacy in Ontario, is $35.00 whereas the ACE costs approximately $20.00. However, there is some variation and any cost savings would obviously be negated if the cost of the ACE were increased or if the Aerochamber were reduced.*

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