Expert Opinion

Targeting drugs to the airways: the role of spacer devices

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Aim: Spacer devices are inhalation aids of varying dimension and complexity, specifically designed to overcome problems with the use of pressurised metered dose inhalers (pMDIs). The aim of this review is to examine the current understanding about these inhalation devices and discuss their advantages and disadvantages. *Methods*: The pertinent literature concerning the characteristics and effects of spacers on delivery and lung deposition of inhaled medications, as well as their clinical efficacy in patients with reversible airway obstruction, is examined. *Results*: Spacers minimise problems of poor inhalation technique with pMDI, reduce oropharyngeal deposition and increase lung deposition. Spacers improve the clinical effect of inhaled medications, especially in patients unable to use a pMDI properly. Compared to both pMDIs and dry-powder inhalers, spacers may increase the response to β-adrenergic bronchodilators, even in patients with correct inhalation technique. A pMDI plus spacer has proven to be viable lower cost alternative to the use of a nebuliser for delivering large bronchodilator doses in patients with severe acute asthma or chronic obstructive pulmonary disease. The use of large-volume spacers is recommended for delivering high doses of inhaled corticosteroids, and may permit a lower maintenance dose to be used. *Conclusion*: pMDIs may be routinely fitted with a spacer, especially in situations where correct pMDI use is unlikely.

Keywords: airways, holding chamber, inhaler, spacer

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1. Introduction

The inhaled route of administration is widely accepted as being the optimal way of giving drugs such as bronchodilators and corticosteroids for the treatment of patients with obstructive airway diseases. Compared with systemic administration, the inhalation route offers a faster onset of action and high *in situ* drug concentrations. This results in a lower required drug dose and subsequent lower rates of side effects [1].

Pressurised metered-dose inhalers (pMDIs) are the most widely used devices for delivering inhaled medication because of their effectiveness, low cost and relative simplicity of use [2]. Despite possessing a number of advantages, pMDIs also have some inherent limitations. First, the spray from pMDIs comprises large rapidly moving propellant droplets which readily impact in the oropharynx, so that no more than ~ 20% of the emitted dose reaches the lungs [1]. Second, many patients do not use pMDIs correctly, despite adequate instruction [3]. Crompton [4] has estimated that as many as half of adult patients and a greater proportion of children are getting little or no benefit from using pMDIs because of poor inhalation technique. The most important errors are dys-coordination between pMDI actuation and inhalation, and the so-called 'cold Freon' effect, which may cause some patients to stop inhaling completely when the cold blast of propellant strikes the back of the throat [3,4]. These errors are particularly important because they can

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Table 1. Advantages and disadvantages of spacer devices.

Advantages	Disadvantages
Reduced hand–breath dys-coordination	Bulkier and less portable than pMDI alone
Reduced systemic and local side effects	More expensive than pMDI alone
Large drug doses delivered more conveniently than using pMDI alone	Require cleaning to reduce electrostatic charge
	Optimal inhalation technique unknown for many spacers
	Not suitable for all types of pMDI canister

result in a reduction of aerosol being deposited in the lung and, consequently, a reduction in the clinical effect [3].

Several inhalation aids have, therefore, been developed to reduce problems of poor inhalation technique with the use of pMDIs [5-7]. The term 'spacer devices' covers a range of inhalation aids of varying dimension and complexity, often known alternatively as 'add-on devices', 'extension devices' or 'holding chambers'. For the purpose of this paper, they will all be described by the term 'spacer'. We will review their characteristics and effects on delivery and lung deposition of inhaled medications; we will also discuss the published data evaluating their clinical efficacy in patients with reversible airway obstruction.

2. Characteristics of spacers

Spacers are extensions to a pMDI with a port at one end to which the pMDI is attached, a face mask or mouthpiece being fitted at the other end. These devices constitute a volume into which the patient actuates the pMDI and from which the patient inhales without necessarily having to coordinate the two manoeuvres. By acting as an aerosol reservoir, these devices slow the aerosol velocity and increase transit time and distance between the pMDI actuator and the patient's mouth, and allow aerosol particle size to decrease [5-7]. As a result, the portion of the aerosol reaching the lung periphery increases [5-7]. Moreover, because spacers trap larger particles comprising up to 80% of the aerosol dose, only a small fraction of the total drug dose is deposited in the oropharynx, thereby reducing side effects such as throat irritation, dysphonia and oral candidiasis; all these unwanted effects have been associated with inhaled medications delivered by the pMDI alone [5-7]. Some spacers are also equipped with valves that generate a whistling sound when inspiratory flow rates exceed a threshold value, above which turbulent conditions lead to excessive impaction of the aerosol dose in the upper airways.

On the negative side, spacers represent an additional cost to the medical system; they are generally bulky, difficult to carry, and the encumbrance of some of them may detract from the appeal of pMDIs to the patients, especially among the paediatric population. Furthermore, some spacers are designed to fit only a single type of pMDI. Moreover, spacers do not completely obviate all errors in inhalation technique; rather, they offer potential for new patient errors, such as incorrect assembly of devices, lengthy delay between pMDI actuation and inhalation from spacer, firing multiple puffs into the spacer before inhaling [8-10]. Spacers are not immune to inconsistent medication delivery caused by electrostatic charge of the aerosol [11-13]. The advantages and disadvantages of spacers compared to the pMDIs alone are summarised in **Table 1**.

Several different types of spacers are commercially available. They differ by volume, length, shape, construction material, rigidity (i.e., rigid or collapsible), presence or absence of the valve system, and interface with the airway opening (e.g., mouthpiece, face mask, adaptor to ventilator tubing).

Generally, spacers fall into three categories (**Table 2**):

1. *open tube spacers*, that simply distance the inhaler mouthpiece from the patient's oropharynx;
2. *holding chambers*, which include a one-way inhalation valve in the mouthpiece, intended to retrain the aerosol within the device until the patient inhales;
3. *reverse-flow devices*, in which the spray is fired away from the patient, either into a collapsible bag or into a small volume through which outside air is entrained.

These varying characteristics of spacers ultimately affect the amount of active agent delivered to the lungs. Bisgaard *et al.* [14] showed that the dose of budesonide delivered from a pMDI plus spacer differed by up to as much as twofold, depending on the type of spacer used. The Nebuchamber™ (AstraZeneca, UK), a metallic, pear-shaped non-electrostatic holding chamber, delivered the highest dose, followed, in descending order of efficiency, by the Babyhaler™ (GlaxoSmithKline Laboratories, France) – a 350 ml plastic cylinder spacer with both inspiratory and expiratory valves – the Nebuhaler™ (AstraZeneca, The Netherlands) – a 750 ml plastic, pear-shaped spacer – and the AeroChamber™ (Trudell, Canada) – a 145 ml plastic cylinder with a single one-way valve [14]. These differences in the delivered dose were likely due to less electrostatic attraction of charged aerosol particles to the walls of the non-electrostatic spacer, as well as to the presence of a separate inspiratory and expiratory valve design of the non-electrostatic spacer [14]. Spacers may perform differently depending upon the particular pMDI to which they are attached. Ahrens *et al.* [15] measured the fine particle dose of β-adrenergic agonists and corticosteroids delivered via the same pMDI attached to four different holding chambers and found that the respirable dose varied with the type of spacer used [15]. These findings suggest the need for further studies to evaluate the interaction between pMDIs and the individual types of spacers with which they are used.

3. Correct use of spacers

Inhalation technique. A number of recommendations can be made for the optimal use of spacers. It is essential that

Table 2. Characteristics of the main types of spacer devices.

Category	Device	Manufacturer	Volume (ml)	Material
Tube spacer	Boeringher spacer	Boehringer, Germany	50	Plastic
	Jet	Chiesi, Italy	100	Plastic
	Azmacort	Aventis	110	Plastic
	Aerovent	Monaghan Medical, USA	145	Plastic
Holding chambers	Aerochamber plus	Trudell Medical, USA	149	Plastic
	Aerochamber MAX*	Trudell Medical, USA	198	Plastic
	Vortex*	Pari, Germany	210	Metal
	Optichamber	Respironics, USA	218	Plastic
	FunhHaler	Infamed, Australia	225	Plastic
	NebuChamber*	AstraZeneca, Sweden	250	Metal
	Rondo	Leiras, Finland	270	Plastic
	Fluspacer*	Menarini, Italy	305	Plastic
	Babyhaler	Allen & Hunburys, UK	350	Plastic
	Volumatic	Allen & Hunburys, UK	750	Plastic
	Nebuhaler	AstraZeneca, Sweden	750	Plastic
Reverse-flow devices	Optihaler	HealthScan, USA	70	Plastic
	Aerosol Cloud Enhancer	DHD, USA	170	Plastic
	InspirEase	Schering, USA	700	Plastic
	E-Z spacer	WE Pharmaceuticals USA	700	Plastic

*Non-electrostatic spacer.

pMDIs containing medications in suspension are shaken before every use since failure to do this reduces drug delivery [16]. Some new pMDI medications are in the form of solution and do not require shaking [17]. The spacer should be positioned before actuating the pMDI because the fallout of aerosol reduces the available dose over time. Movement of the spacer should also be avoided, as this will reduce the drug available for inhalation due impaction on the sides of the spacer wall [18]. Generally, patients using pMDIs with a spacer still have to be trained to inhale slowly (≤ 30 l/min) and to hold their breath after aerosol inhalation for at least 10 sec [6]. A too long delay in inhalation after pMDI actuation may lead to excessive loss of the respirable dose within the device [9]. Some patients tend to discharge multiple doses from a pMDI into a spacer before inhalation. The turbulence created by this practice leads to coalescence of small particles into larger particles and subsequent excessive deposition on the walls of the spacer, thus reducing the respirable dose per actuation [10].

The inhalation technique adopted when using a pMDI with a spacer affects drug delivery. Package inserts for large-volume spacers typically advise taking one or two deep inhalations from the device after firing a single dose. O'Callaghan *et al.* [19] assessed the mass of sodium cromoglicate delivered in respirable (< 5 µm) particles from a 750 ml spacer. Compared with actuating a single dose into the spacer and then inhaling, firing multiple doses and then inhaling these doses in a single breath reduced drug delivery [19]. Thus, if multiple drug doses are prescribed, they should be given separately. Slow inhalation is preferable since the impaction of particles is proportional to velocity and particle size [20]. A slow inspiratory flow reduces the risk of impaction on spacer valves and anatomic structures such as the pharynx or vocal cords. In addition, high inspiratory flow rates enhance central deposition caused by inertial impaction and therefore reduce deposition in peripheral airways [20]. Large-volume spacers can be used by firing a dose into the device and then inhaling after a short pause, but a reduction in drug delivery was observed by increasing the delay time between actuation and starting to inhale. A 20 sec delay time reduced drug delivery by two-thirds [8]. Taking multiple tidal breaths from a large- volume spacer may be more practical than taking single deep breaths, especially in children, and this appears to result in satisfactory bronchodilator response [21]. The number of breaths required to empty a spacer obviously depends on the size of the device, as well as on the patient's characteristics. Adults may empty a spacer in one or two inhalations, whereas commonly used spacers for young children were emptied in two to four breaths [22]. Bisgaard *et al.* [20] recommend 10 breaths in infants, five breaths in toddlers and two slow deep inhalations in older children and adults.

The correct inhalation technique for pMDIs with attached spacers is reported in **Table 3**.

Spacers and HFA-driven inhalers. Many current pMDIs have moved from chlorofluorocarbon (CFC) propellants. The production and use of CFC propellants has been stopped in most developed countries because of the effect on the ozone layer. The challenge has been to develop safe alternatives that are as convenient, effective and clinically equivalent. The process of development of alternative propellants has been more of a problem than first appreciated, particularly for inhaled steroids. Adaptations to the method of adding the drug to the propellant and to the valve and jet mechanisms

Table 3. Inhalation technique with pMDIs plus spacer.

Steps to follow	Explanation and references
Remove the cap from pMDI and spacer	
Shake the pMDI and connect it to the spacer, keeping the inhaler upright	For inhaled drugs in the form of suspension, shaking the inhaler before each use ensures homogenous and uniform dose [16]. Some new products are in the form of solution and do not require shaking [17] If the pMDI is being used for the first time or has not been used for over 1 – 2 weeks, the dose medication may have escaped from the metering chamber and a full dose may not be obtained on initial actuation; therefore, the pMDI should be primed [6]
Spacer with mouthpiece: place the spacer between the teeth and seal the lips around the mouthpiece Spacer with face mask: place the mask over face making sure that the mouth and nose are covered and that the seal is as airtight as possible without undue discomfort	
Exhale to near residual volume (RV)	Expiration until RV may help the patient to take a deep breath in
Actuate the canister once and begin inhaling slowly until total lung capacity	Inspiration should begin no later than 3 sec after pMDI actuation because once the medication is aerosolised it remains suspended in the spacer for less 10 sec [6] A slow (inspiratory flow < 30 l/min) deep inhalation is recommended [6]. Some spacers (i.e., Aerochamber Plus) have a special sound feature that indicates when inspiration is too rapid
Single-breath technique: hold the breath for 10 sec	Breath holding increases the staying time of the particles in the lungs, thus increasing deposition by means of sedimentation and diffusion [6]. A 10-sec breath holding is more effective than 4 sec pause; however, breath holding longer than 10 sec yields no additional benefit [6]
Tidal volume technique: breath slowly in and out of the spacer 3 or 4 times in a row	The tidal volume technique is an effective alternative for patients when using a holding chamber but unable to perform the single-breath technique [39]. Since the one-way valve closes during expiration, there is no risk of drug dispersion
If another dose is required, repeat steps 2 to 6	Some patients try to save time by spraying more than one dose into the spacer at one time, but this decrease the total amount of the drug reaching the lungs [19]

have been necessary. Hydrofluoroalkanes (HFA) 134 and 227 are used in the new inhalers, and β-adrenergic bronchodilators, inhaled steroids and combinations are now available in inhalers with HFA propellants. With the redesign of pMDIs to contain HFA propellants instead of CFCs, system improvements have resulted in pMDIs with much lower impact force and throat deposition and greater deposition in the lungs than CFC-driven inhalers [23]. In addition, patients may find that pMDIs with HFA propellants have a different taste and feel because the spray emitted from the actuator has less forceful and a smaller plume [24]. In theory, these plume characteristics could reduce the likelihood that patients will experience the cold-Freon effect, that is stopping the patient inhaling or prompting inhalation via the nose when the cold forceful blast of propellant impacts on the back of the patient's throat. Gabrio *et al.* [25] have compared plume characteristics of both CFC- and HFA-driven pMDIs delivering several marketed bronchodilators or steroids. They found that, despite most HFA-driven pMDIs producing softer plumes than CFC-driven pMDIs, the use of HFA propellants does not guarantee better results independently of the drug employed. For example, Proventil™ (Schering-Plough Corporation, USA) HFA and Beclazone™ (Teva, UK) HFA produced significantly softer plumes than all of the corresponding CFC products. However, Sultanol™ (GlaxoSmithKline, UK) and Futide™ (GlaxoSmithKline, UK), which also use HFA propellants, had very high spray forces due to their use of large orifices [25]. This finding illustrates that the plume characteristics and, consequently, the cold-Freon effect, are dependent on the entire pMDI system.

The different spray characteristics of HFA-driven inhalers may affect drug delivery to the lungs when the inhaler is used with an attached spacer. However, the effects of spray differences between HFA and CFC pMDIs on their performance with spacers has not been adequately explored. Moreover, the interaction of HFA-driven inhalers with spacers is complicated by differences in spacer characteristics [26] and formulations within the inhaler, as well as by the development of electrostatic charges, which increase the deposition of albuterol within the spacer. Joguparthi *et al.* [27] have

shown that, due to its less forceful spray and smaller plume, HFA-driven inhalers may deposit a smaller amount of albuterol in the spacer; consequently, more albuterol may be inhaled [27]. More recently, Roller *et al.* [28] have shown that inhalation of beclometasone dipropionate extra-fine particles delivered via an HFA-driven inhaler with an attached spacer (Aerochamber Plus™, [Trudell, UK]) resulted in a high lung deposition and marked decrease in oropharyngeal deposition compared with delivery of the same formulation via the HFA-driven inhaler alone. Similarly, Nair *et al.* [29] have demonstrated that the use of HFA-driven pMDI in conjunction of a prewashed and primed spacer significantly increased the respirable dose delivery of fluticasone propionate compared with pMDI alone. Taken together, these findings suggest that the addition of spacers to HFA-driven inhalers reduces the incidence of local adverse effects, such as oral candidiasis and dysphonia, improves drug delivery to the lungs and, possibly, clinical efficacy.

Control of static charge. Almost all spacers are constructed of plastic, the surface of which may accumulate static charge. The net effect of this electrostatic charge is attraction of aerosol particles onto the plastic surfaces of the spacer. This will significantly reduce the aerosol dose available for inhalation. Drug delivery from spacers may be increased by placing an antistatic lining on the inner walls of the device [19], as well as by appropriate spacer washing techniques [12]. For example, Dewsbury *et al.* [30] found that washing the spacer in soapy water, rinsing in tap water, and then allowing to air dry, resulted in the lowest static voltage on the spacer surface and the highest respirable dose. Repeated use of the pMDI itself primes the plastic surface of the spacer to some extent, thereby reducing electrostatic charge [31]. However, this practice is not currently recommended, mainly because of the waste of the medication and thus cost. Some newly marketed spacers are constructed of non-electrostatic material. For instance, the Nebuchamber is made of lightweight metal that is not susceptible to static charge accumulation. It has been shown that deposition of budesonide in the lungs increased from about 25% using plastic spacers to about 35% when Nebuchamber was used [31].

Despite laboratory studies showing that electrostatic charge has a deleterious impact on spacer performance, the clinical evidence is less clear. Anhøj *et al.* [32] observed that the charge associated with two non-conducting spacers, washed but rinsed afterwards, reduced lung deposition in children by a factor of more than twofold. This finding was associated with significant decreases in plasma salbutamol concentrations. In asthmatic adults, Wildhaber *et al.* [33] showed an improvement in bronchodilator response after reducing the electrostatic charge of a spacer by washing it with household detergent. Similar results have been obtained also with HFA-driven inhalers [34]. In contrast, Dompeling *et al.* [35] reported no significant differences in bronchodilator responses after salbutamol administered via two prewashed, non-conducting spacers (the Volumatic™ [Allen & Hanbury's, UK] and the Aerochamber) or via electrically conducting spacer (the Nebuchamber). More recently, Dubus *et al.* [36] also found little difference in lung function outcomes measures using non-conducting or conducting spacers when administering salbutamol in asthmatic children. However, the authors observed that the drug doses used in the study were at the plateau of the dose-response curve, and that methacholine challenges, the method used to assess airway responsiveness, does not mirror an asthma attack [36]. In reviewing the clinical evidence, Le Souëf stated that the increase in performance associated with detergent pre-treatment of spacers manufactured from non-conducting material is almost certainly important for inhaled corticosteroids [37]. Clinicians should, therefore, be aware of ways to minimise or avoid electrostatic charge when prescribing spacers, given the possibility that underdosing for some formulations may occur if significant charge is present.

4. Effects of spacers on drug deposition

Compared with the pMDI alone, spacers markedly reduce oropharyngeal drug deposition [5]. The reduction in oropharyngeal deposition arises because spacer devices have a size-selective function, by which a proportion of particles that would have been deposited in the oropharynx is transferred to the spacer itself [5], whereas smaller particles are allowed to reach the patient's airway. The results of studies on the effects of spacers on pulmonary deposition of inhaled drug are somewhat controversial [5]: while some studies have demonstrated an increase in lung deposition with spacers, other studies have failed to demonstrate significant differences compared with the pMDI alone. Several factors are likely to account for these variable findings. For instance, the inhalation techniques used, as well as the amount of electrostatic charge present in the spacer, may affect drug delivery and, consequently, lung deposition [5-7]. Differences in the radiolabelling methods employed in the studies may also play a role [6]. For these reasons, caution should be taken in comparing data derived from lung deposition studies performed with different spacer devices.

Spacers vary widely in their shape and size, with volume ranging from 50 to 750 ml. Although this is not an invariable rule, large-volume spacers appear to increase lung deposition to a greater extent than small-volume tube spacers [5-7]. Many spacers have a one-way valve which may influence drug deposition in the lungs. The valves that operate on inhalation and exhalation must function effectively over the entire pressure range likely to be encountered with the use of a spacer. This requirement is unlikely to be a problem for adults, since the pressure required to operate valves of most spacers is less than 300 Pa [38]. However, it may become an issue for neonates or infants if the valves are stuck closed. The amount of drug deposited in the lungs depends upon the nature of the aerosol formulation used with a given spacer, or upon the type of spacer used to deliver a given

formulation. For example, Matthys [39] has shown that when a radiolabelled formulation of sodium cromoglicate was given via three different spacers, the drug dose deposited in the devices, oropharynx and lungs varied widely between the three spacers. Conversely, administration of three different drug formulations delivered via the same spacer resulted in significantly different values of lung deposition [39].

As reported above, the inhalation technique is another factor that affects aerosol deposition. Ernst has reported that, for efficient use of pMDIs, the patient should inhale slowly and continuously followed by a breath-holding of at least 10 sec [40], thereby allowing the aerosol to penetrate deeply into the lungs [41]. Guidance on the GINA guidelines for the use of the Aerochamber spacer is based on this inhalation technique, but slow inhalation and tidal breathing modalities are recommended for the Volumatic spacer [42]. Younger children using a face mask are able to breathe tidally, and indeed this is likely to be the optimal modality for infants [38]. Until recently, no study with children has systematically examined issues such as the optimal time of inhalation and whether the patient should use tidal breathing or the long slow inhalation technique when using a spacer. However, Roller *et al.* [28] have recently been reported that, in children aged from 5 to 17 years, for inhalation of beclometasone in extra-fine formulation (mass median aerodynamic diameter about 1 μm), slow inhalation to vital capacity followed by a breath-hold of at least 5 sec showed improved lung deposition compared with tidal breathing. Further studies are needed to investigate if similar results might be obtained with aerosol formulations containing larger particles (mass median aerodynamic diameter about 5 μm).

5. Effects of spacers on clinical responses

Despite the large numbers of clinical trials performed with a variety of spacers in patients with obstructive airway diseases, there are still difficulties in demonstrating differences in the clinical responses between spacers and other inhalation devices [43]. Part of the confusion stems from the fact that the inhalation techniques used in some studies are inadequately controlled or inadequately described. It has been reported [43] that, if a patient is using the simple pMDI appropriately, spacers do not add additional benefits; whereas, if someone is using the pMDI ineffectively, a spacer may make the difference between a good and poor therapeutic effect. König [43] described this situation by referring to spacers as neither a 'gimmick' nor a 'breakthrough', but as having a role somewhere between these two extremes. In keeping with this possibility, some studies have failed to show differences in the clinical response between spacers and other inhalation devices, possibly because these studies had insufficient power to detect a difference of clinical significance, or because they are conducted close to the plateau of the dose–response curve [5-7]. Even if a spacer is found to be more efficacious than other inhalation devices in a well-designed clinical trial, it should be remembered that subjects who agree to take part in such trials may have received extensive coaching in spacer use. As such, they may not be typical of the general population. In addition, changing from one spacer to another may be of scarce importance with some drugs but critical for others, leading to overtreatment or treatment failure. Furthermore, the effect of electrostatic charge may also affect the clinical response to inhaled medications administered via pMDIs plus spacers [34,39]. For these reasons, clinicians should be aware that data about a spacer derived from clinical studies with one drug may not apply to others.

In the following sections of this review we will summarise the published studies comparing the clinical efficacy of spacers with that of nebulisers, pMDI alone and dry-powder inhalers (DPIs).

5.1 Spacers versus nebulisers

Several clinical studies [2,44-46] have shown that spacers are at least as effective as nebulisers in the treatment of patients with severe acute asthma attacks and hypoxemia, with a dose ratio of about 1 to 6 in favor of spacers. Furthermore, use of spacers was associated with a lower pulse rate increase than nebulisers, possibly due to a lower total dose of β_2-adrenergic bronchodilators [46]. Advantages of spacers over nebulisers include improved delivery efficiency, greater convenience, an inherently lower risk of pulmonary infection, greater speed of administration and cost-effectiveness. Holding chambers, such as the Babyhaler, equipped with face masks, are a useful alternative to nebulisers in delivering inhaled medications to infants and children with asthma [5,45]. In these patients, the use of holding chambers rather than nebulisers for delivering inhaled medications results in a more rapid discharge from the hospital and a reduction in drug-related costs [47-48].

5.2 Spacers versus pMDIs alone

There is a wealth of studies [5,43,49-53] that have investigated the clinical efficacy of spacers compared with that of pMDIs alone. In terms of bronchodilation, some studies [49-50] suggest that spacers do not confer any additional benefit when the pMDIs alone are correctly used; in contrast, other investigations [51-53] show that, compared to the pMDI alone, spacers do enhance bronchodilation. It is likely that the favourable results obtained with spacers in some studies may be due to the inclusion of patients with poor inhalation technique. In other studies, the detection of an additional bronchodilator effect exerted by spacers may be impeded, at least partially, by factors such as the bronchomotor effect of the deep inhalations required for assessing bronchial responses, the method(s) used to quantify them and differences in baseline airway calibre. In asthma patients who correctly operate a pMDI we have compared the effects of administration of a β_2-adrenergic bronchodilator through the pMDI alone and two different spacers (the large-volume spacer Volumatic, and the small-volume spacer Jet™ [Chiesi Farmaceutici, Italy])

on the magnitude and velocity of large and small airway bronchodilator response [53]. We found that, even in patients with good inhalation technique, both spacers enhanced bronchodilation compared to the pMDI alone. Furthermore, compared with both the Jet and the pMDI alone, the Volumatic allowed faster and larger small airway dilation with less than half the dose of the bronchodilator drug [53].

As regards inhaled steroids, it has been shown that in severe asthma patients who require high doses of beclometasone dipropionate, the addition of a spacer to the pMDI not only markedly reduced the incidence of oral candidiasis, but also resulted in a continuing trend of improvement in airflow obstruction over 3 – 6 months, which did not occur in patients using the pMDI alone [54]. It is of note that the British Asthma Guidelines [55] recommend the use of large-volume spacers for delivering high doses of inhaled corticosteroids (> 1000 mcg/day for beclometasone, > 500 mcg/day for fluticasone) in asthma patients.

5.3 Spacers compared with dry powder inhalers

Studies aimed at ascertaining whether differences exist in the clinical response to administration of inhaled medication via a pMDI plus spacer or via a dry powder inhaler (DPI) have yielded conflicting results [2]. For example, a recent study [56] performed in asthma and COPD patients with moderate-to-severe airway obstruction suggests that the magnitude of bronchodilation following salbutamol administered via a spacer is greater than that obtained by using two different DPIs. However, the differences are minimal and, in the authors' view, of no clinical significance. Other studies [57-58] performed in asthma children suggest that terbutaline is equally effective when administered via a spacer or via a DPI, the Turbuhaler™ (AstraZeneca, Sweden), at the same nominal dose. Studies with inhaled corticosteroids [59-60] support the equivalence of budesonide administered via a spacer or via a Turbuhaler, but the latter at half of the nominal dose for the spacer. Dissimilarities in the types of inhalation devices, the inhalation methods used and the characteristics of the patients studied may account for these conflicting results. Recently, we undertook a study to compare the magnitude and time course of changes in lung function and dyspnoea intensity following different salbutamol doses inhaled via a DPI, the Diskus™ (GlaxoSmithKline, UK), or via the Volumatic spacer in asthma patients [61]. This study was carried out in patients with induced, rather than spontaneous, bronchoconstriction to obtain a standardised level of reduction in baseline airway calibre, thus avoiding the confounding effects related to different degrees of natural bronchoconstriction. We found that the magnitude of salbutamol-induced changes in FEV_1 and dyspnoea intensity score was unaffected by either the salbutamol dose or inhalation devices, possibly because, even with the lower salbutamol dose, the responses had already reached the plateau of the dose–response curves [61]. However, increases in small airway patency and lung volumes induced by salbutamol were markedly higher in Volumatic than Diskus trials [61]. The same inhalation devices have been compared in a subsequent study [62] aimed at evaluating the speed of the bronchodilator response following salbutamol administered via these devices in asthma patients. We found that salbutamol via the Volumatic provided faster reversal of induced bronchoconstriction than via the Diskus (**Figure 1**). Furthermore, twice the dose of salbutamol administered via the Diskus was needed to obtain a magnitude and velocity of bronchodilation similar to those obtained when the drug was administered via the Volumatic spacer (**Figure 2**), thus suggesting that these two salbutamol formulations could not be considered therapeutically equivalent [62-63]. Furthermore, studies performed in asthmatic children [64,65] have suggested a 1 to 2 potency ratio for budesonide delivered via the pMDI plus the large-volume Nebuhaler spacer, compared to the Turbuhaler. On the basis of these findings, care should be taken by physicians when a patient is switched from one inhaled product to the same drug dose from a different inhaler.

6. Pharmacoeconomic aspects

The therapeutic equivalence per dose cost of pMDI-generated bronchodilators and steroids has been shown to be generally lower by a factor of one to twofold or more than other devices for aerosol administration [7]. A number of studies [47,48,66-69] have stressed the cost benefits of switching from small-volume nebulisers to pMDI with spacers for treating reversible airflow obstruction in hospital and at home. Bowton *et al.* [67], based on a cost analysis of switching their 600 bed tertiary referral hospital from small-volume nebulisers to holding chambers, estimated annual savings at about US$400,000. By extrapolating to other similar hospitals in the USA, they concluded that the annual savings on this therapeutic modality could amount to about US$200 million. This was further supported by a meta-analysis showing a 30% cost benefit by using pMDIs instead of small-volume nebulisers in the emergency department [69]. Given the large amount of evidence in favour of using pMDI plus spacers to generate bronchodilator aerosols for the rescue of patients with acute asthma attacks treated in the emergency department and taking into account savings in time and cost, it is surprising that the nebulised route of administering bronchodilators is still the dominant route for the treatment of asthma patients attending emergency departments [69]. The reasons why the nebulised route is still used is not known, but it is likely to reflect a long-term practice. With increasing emphasis on cost control, however, this situation is changing, but change is unlikely to be accomplished rapidly in any given hospital without an advocate, usually to be found among knowledgeable physicians or respiratory technologists.

7. Conclusion

More than 20 years ago, König [43] posed the question whether spacers represented a 'breakthrough' or a 'gimmick',

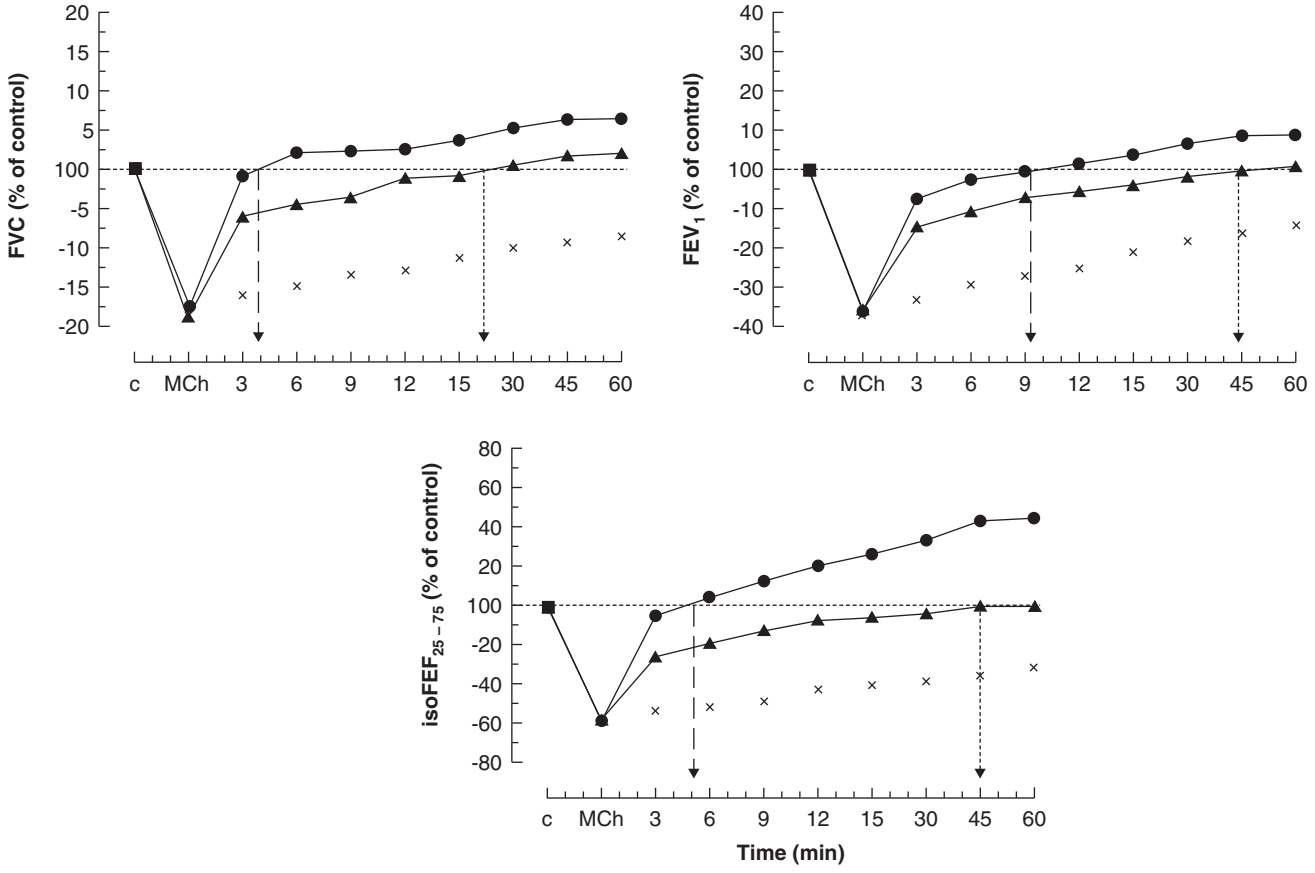

Figure 1. Changes in post-methacholine (Much) forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and volume-adjusted forced expiratory flow rate between 25 and 75% of the FVC ($isoFEF_{25-75}$) following administration of placebo (X symbols), and 400 µg (filled symbols) of salbutamol through the pMDI + Volumatic spacer (circles) and the Diskus (triangles). In each panel, the thick dotted line marks the control (pre-methacholine) value of each considered variable. The arrowed line indicates the times needed to attain the control (C) values of each considered variable following salbutamol administration via pMDI + Volumatic (dashed arrows) and via Diskus (dotted arrows).
Modified from Ref [62].

and concluded that they were neither a breakthrough of such magnitude that they should be made mandatory for all pMDI users, nor a useless gimmick, but that they had a value somewhere between these extremes. We believe that this is not the situation pertaining today. In fact, several studies have demonstrated the effectiveness of a bronchodilator administered via pMDI plus spacer in the treatment of acute severe asthma in both children and adults. Furthermore, we have shown that [53,61-63] large-volume spacers, compared to both pMDIs alone and DPIs, may increase the bronchodilator response, even in patients with correct inhalation technique. In addition, spacers reduce problems of poor inhaler technique with pMDI and largely eliminate oral absorption of inhaled corticosteroids [55]. Thus, based on these considerations, we believe that every pMDI may be routinely fitted with a spacer, especially in situations where correct pMDI use is unlikely.

The 21st century will undoubtedly see further advances in devices for delivering inhaled medication to patients with obstructive airway disease and for monitoring and assisting adherence to prescribing inhaler use. As regards spacers, the challenges for the 21st century will be to develop user-friendly devices that are specific to particular pMDIs and to evaluate the delivery of respirable doses from the spacer–inhaler combinations.

8. Expert opinion

National [55] and international [42] guidelines recommend the inhaled route as the preferred method of delivery for medications to treat airway obstructive diseases. However, to be successful and cost-effective, drug aerosol delivery has to be targeted. Maximum deposition of suitable therapeutic aerosol particles at the level of airways minimises potential drug side effects and reduces healthcare cost with increased efficacy. An example for the need of optimal drug aerosol targeting is asthma, although conventional inhalation therapy

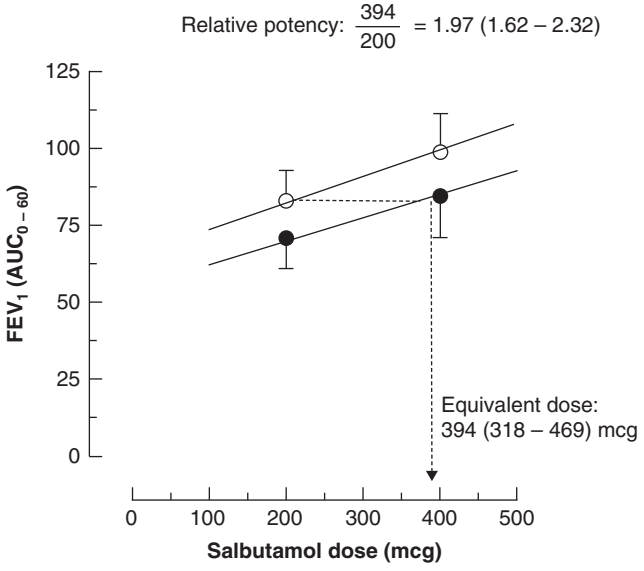

Figure 2. Therapeutic equivalence between salbutamol administered via pMDI + Volumatic and via Diskus in asthma patients. The arrowed line indicates the calculated salbutamol dose to be delivered by the Diskus to achieve forced expiratory volume in 1 s (FEV_1) values equal to those observed following 200 mg salbutamol administered via the pMDI + Volumatic. Relative potency is expressed as the ratio of the salbutamol doses to be delivered by the two inhalation devices to achieve similar FEV_1 values.
Modified from Ref [63].

is widely considered to be sufficient. Asthma therapy relies on anti-inflammatory corticosteroids and long-acting β_2-agonist bronchodilators, typically delivered in droplet spray or powder form with off-the-shelf inhalers [42]. Nevertheless, the morbidity and mortality from asthma seems to be rising, despite better understanding of the pathogenesis of the disease, more awareness of under-diagnosis and under-treatment, and a wide choice of effective treatments. Surveys of the severity of symptoms show that up to 50% of patients fail to achieve good control of their symptoms, while 60 – 80% are unable to gain total control of the disease [70]. The main reasons for this failure are the limitations of current inhalation therapy, including shortcomings in drug effectiveness and inhaler efficiency [71]. These shortcomings imply the inability of the drugs to reach their site of action in the airways, especially the peripheral airways, which are considered a major site of pathology of asthma. Furthermore, poor inhaler technique could account for this, although poor adherence to prescribed treatment is also a problem [3,4,72].

Pressurised metered-dose inhalers are the most widely prescribed inhaler devices. Despite numerous advantages, pMDIs are inefficient since no more than 20% of the emitted dose reaches the lungs, with a high proportion of drug being deposited in the oropharynx which can cause local, as well as systemic side effects, due to rapid absorption [5-7]. To overcome these problems, aerosol research has resulted in the development of spacers with a variety of sizes, shapes, presence or absence of valves, and made from a variety of materials. Spacers are add-on devices that interface with the actuator/mouthpiece of the pMDI, providing additional space for the aerosol plume to develop. Spacers help the patients to overcome the problems of poor inhalation technique associated with the use of pMDIs. This is especially valuable in treating elderly patients and children and is a more economical response to the problem than prescribing the more costly DPIs. For asthma, the GINA guidelines [42] draw attention to the requirement for coordination of pMDI actuation with inhalation, and recommend the use of spacers, particularly in children. In infants and preschool children, in whom active cooperation cannot be expected, a pMDI used with a spacer and face mask is recommended as the device of choice for maintenance treatment. As cooperation improves, often around the age of 4 to 6 years, it further recommends that the child is encouraged to use a mouthpiece rather than face mask attachment to the spacer [20,38,73]. Furthermore, spacers are also recommended for delivering inhaled corticosteroids, especially those with a low first pass metabolism, at any age [20,38,73], and this may permit a lower maintenance dose to be used [55]. The current authors' policy is to use spacers, particularly valved anti-static holding chambers, across the spectrum of the patient population, from infants to the elderly. Valved holding chambers allow the patients to breathe tidally from a reservoir of drug, thus reducing the need of coordination between inhaler actuation and inhalation. Although the introduction of a spacer for a pMDI to the patient does not abrogate the physician's responsibility to teach patients the proper aerosol administration with it and to re-examine their inhalation technique on subsequent visits, we believe that every patient who uses a pMDI should have a spacer and know how to use it. Furthermore, package inserts for pMDIs should inform patients of the value of spacers in enhancing the effectiveness of inhalers, especially during exacerbations.

Different spacers are often marketed for use with a particular manufacturer's drug or range of drugs, and studies often compare the effect of different drug–device combinations, making it difficult to determine the contribution of the spacer device alone on efficacy. In general, both large-and small-volume spacers reduce oropharyngeal deposition and the potential for systemic absorption [74]. However, large-volume spacers appear to increase lung deposition to a greater extent than small-volume spacers [74]. Inhaled corticosteroids are cornerstones in the management of obstructive airway diseases. Since these drugs are relatively costly and have a narrow therapeutic index, it is essential that the nominal (labelled) dose delivered is optimized, with a high proportion of fine particles. Moreover, inhaled steroids are normally given twice daily and, therefore, portability is less of an issue than with bronchodilators. For these reasons, optimal designed spacers, such as large-volume, anti-static holding chambers, are essential

for delivery of inhaled steroids. As regards bronchodilators, the dose of bronchodilators in commercially available pMDIs is several times higher than those that produce maximal effects on airways [5-7] Therefore, it may be possible to lose a large proportion of the drug through poor inhalation technique, while still obtaining maximal bronchodilation. Indeed, some bronchodilators are used on an 'as-needed' basis. Therefore, small-volume tube spacers may be used for bronchodilator administration.

From a clinical point of view, large-volume spacers are at least as effective as nebulisers for giving high doses of bronchodilators in acute severe asthma [46-48]. Unlike nebulisers, they are widely available, cheap, easily portable and do not require electricity. In addition, recent data from our laboratory [53,61-63] suggests that, compared to both pMDIs alone and DPIs, large-volume spacers may increase the response to short-acting β-adrenergic bronchodilators, even in patients with correct inhalation technique. Differences in clinical responses to bronchodilators delivered via different spacer devices have been described in some studies but not all, perhaps because the dose of drug delivered tends to fall on the flat part of the dose–response curve [2, also for further refs]. In a study performed in asthma patients, we found that both the small-volume Jet spacer and the large-volume Volumatic spacer caused larger FEV_1 increases compared to the pMDI alone [53]. However, compared with the Jet, the Volumatic allowed faster and larger small airway dilation with less than half the dose of the bronchodilator drug [53]. Thus, large-volume spacers appear to be equally or more effective than smaller spacers, unless the more 'user friendly' smaller spacers are more acceptable to the patients, especially for bronchodilators used on an 'as-needed' basis. While the efficiency of these devices may vary from one to another and engineers are likely to opt for the most efficient, which are usually the largest, clinicians have to take other factors into account (such as pocketability, ease of assembly and use, durability and universality) to obtain optimum patient compliance.

In conclusion, spacers largely reduce problems of poor inhaler technique, improve the therapeutic index of aerosol treatment and reduce the cost of treatment The advantages of spacers could feature more prominently in future asthma and COPD guidelines, and pharmaceutical companies should devote part of their advertising budget to making patients and doctors more aware of the role of these devices. By reducing the enormous waste of inhaled drugs that result from poor inhaler technique, the respiratory prescribing costs would be reduced. More importantly, the use of spacers should improve the effectiveness and efficiency of the management of asthma and COPD and so help to reduce morbidity, the need for admission to hospital and perhaps even mortality.

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