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Spacers and Valved Holding Chambers – the risk of switching to different chambers

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Abstract

Spacers are pressurized metered-dose inhaler (pMDI) accessory devices developed to reduce problems of poor inhaler technique with pMDIs. Spacers that feature a one-way inspiratory valve are termed valved holding chambers (VHCs); they act as aerosol reservoirs, allowing the user to actuate the pMDI device and then inhale the medication in a two-step process that helps users overcome challenges in coordinating pMDI actuation with inhalation. Both spacers and VHCs have been shown to increase fine particle delivery to the lungs, decrease oropharyngeal deposition, and reduce corticosteroid-related side effects such as throat irritation, dysphonia, and oral candidiasis commonly seen with the use of pMDIs alone. Spacers and VHCs are not all the same, and also are not interchangeable: the performance may vary according to their size, shape, material of manufacture and propensity to become electrostatically charged, their mode of interface with the patient, and the presence or otherwise of valves and feedback devices. Thus, pairing of a pMDI plus a spacer or a VHC should be considered as a unique delivery system. In this Rostrum we discuss the risk potential for a patient getting switched to a spacer or VHC that delivers a reduced dose medication.

Abbreviations used

VHC: valved holding chamber;

pMDI: pressurised metered-dose inhaler;

EMA: European Medicines Agency;

FDA: US Food and Drug Administration;

98 Pressurised metered-dose inhalers (pMDIs) are the most widely used devices for delivery of
99 aerosol medications due to their effectiveness and relative simplicity of use [1]. However, an
100 important weakness of pMDIs is their propensity to be used sub-optimally or incorrectly [2], a
101 problem that has been recognised since their inception and that is unfortunately still present today
102 [3]. In a survey conducted among persons referred by family physicians, internists, surgeons and
103 pulmonologists for routine spirometry only 10.8% of the subjects correctly performed all the
104 manoeuvres recommended for self-administration, and 24.7% failed to perform more than half the
105 manoeuvres adequately [4]. A review of 2123 asthma patients by the National Services for Health
106 Improvement found that, without training, 86% failed to properly use their inhaler [5]. Even with
107 inhaler training, some people will revert to bad technique, and some will not benefit from training
108 [6]. One of the most common error associated with pMDIs is the lack of coordination between
109 inhaler actuation and inhalation [2]. Coordination between inhalation and generation of the aerosol,
110 so that inhaler should be activated just after onset of inspiration, is crucial to increase drug
111 deposition in the lung during pMDI use [7]. In the CRITIKAL study, poor coordination between
112 inhaler activation and inhalation led to a greater likelihood of uncontrolled asthma symptoms and a
113 higher rate of exacerbations [8].

114 Spacers and valved holding chambers (VHCs) are medical devices, made of either polycarbonate
115 plastics or metal, which interface with the pressurised metered-dose inhaler (pMDI). They are
116 shaped like a tube with openings at both ends: one opening is the mouthpiece that is placed into the
117 mouth (or a facemask fitting the spacer with a tight seal) and the other opening is where the pMDI
118 is inserted [9-11]. In this way, they provide additional space for the aerosol plume to develop [9-
119 11]. In fact, with either a spacer or a VHC, the aerosol flows from the pMDI into the chamber, thus
120 allowing deceleration of the aerosol plume and, in the case of VHCs, trap the aerosol cloud until the
121 patient inhales from the chamber rather than directly from the pMDI [9-11]. This greatly reduces
122 oropharyngeal drug deposition via retention of large aerosol particles within the holding chamber
123 thus reducing the potential for corticosteroid-related local side effects (i.e. candidiasis and

dysphonia) and systemic absorption [9-11]. Although the terms “spacer” and “VHC” are frequently used interchangeably, the former is a generic term for any open tube, sometimes made from household items such as toilet paper rolls or plastic soda bottles [12, 13], placed on the mouthpiece of pMDI to extend its distance from the patient’s mouth [9-11]. On the other hand, a VHC is a spacer that is manufactured with a one-way, low resistance valve to regulate inspiratory flow and prevent exhalation into the device [9-11]. The newer VHCs such as the AerochamberFlow-Vu (Trudell Medical International, Canada), the OptiChamber Diamond (Philips Respironics UK) or the InspiraChamber (Lupin Pharmaceuticals, India) have an alert whistle to provide feedback on correct inspiratory flow [14]. The VHCs are generally preferable to simple spacers since the latter, due to the lack of a one-way valve, are susceptible to dispersal of the aerosol within due to uncoordinated exhalation into the chamber. In addition, VHCs also substantially lessen the need of inhaler actuation-inhalation coordination, which is problematic for both adults [1,2] and children [15]. As a result, VHCs may increase pulmonary deposition of drug suspensions [16] and, compared to the pMDI alone, may improve clinical outcomes including airway hyperresponsiveness [17], lung function [18-20] and asthma control [21], with a reduction in the requirement for oral corticosteroids [22]. Accordingly, use of VHCs is firmly recommended in international guidelines on the management of asthma [23-25] and chronic obstructive pulmonary disease [26] (Table 1), particularly in patients prone to pMDI handling errors [27]. Although patients who have correct technique with pMDIs may not derive any benefit from use of VHCs [27], the latter reduce oropharyngeal deposition of large aerosol particles emitted from a pMDI, even with “perfect” technique [28]

While the potential benefits of spacers/VHCs are clear, there is less consensus as to whether there are any meaningful differences between different devices. There is substantial, occasionally contradictory, literature detailing the relative performance of a large number of different spacers or VHCs [29]. It is well established from *in vitro* studies that a specific VHC may perform differently with different drugs [30-32] or a specific drug may perform differently in terms of emitted fine

150 particle mass if inhaled through different VHCs [33]. Thus, substitution of one type of spacer or
151 VHC with another may have both safety and clinical implications unless otherwise proven as
152 equivalent through *in vitro* and/or *in vivo* studies. Hatley et al [34] found that the aerodynamic
153 particle size distribution of albuterol aerosols obtained by two antistatic VHCs were similar but
154 significantly different from that obtained by using a conventional VHC. Recently, D’Vaz and co-
155 workers reported no difference in the bronchodilator response, as assessed by FEV₁ changes, to
156 salbutamol inhaled through different spacers in asthmatic children [35]. Accordingly, radiolabelled
157 aerosol studies found equivalent lung deposition of aerosol using different spacers [36]. However,
158 detection of differences in the bronchodilator response to an agent delivered by different devices
159 may be difficult due to the potentially confounding effects related to the patient inhalation
160 technique, as well as to the variability of the levels of airway narrowing, especially when such
161 variability is not adequately accounted for in patient selection [18, 19]. In addition, even low doses
162 of bronchodilators delivered by virtually any inhalation device may produce near maximal
163 bronchodilator responses falling on the flat part of the dose-response curve [18, 19, 37]. Although
164 some studies failed to show significant differences in lung deposition between different
165 spacers/VHCs [36], others found that large-volume (greater or equal than 750 ml) greater whole
166 lung deposition compared with smaller devices [38]. Differences in the study design and
167 methodology may account for these contradictory results.

168 Dissanayake et al [39] set out to address the impact of spacer design on drug delivery
169 performance and look at potential implications for clinical use. Four similarly sized chambers were
170 compared ‘out of the box’ in terms of statistical equivalence with the most widely prescribed, non-
171 conducting VHC, Aerochamber Plus[®] chamber (Trudell Medical International, Canada) with
172 respect to retention of drug particles within the device and the aerodynamic particle size distribution
173 of the drug particles delivered. The authors found that only the Aerochamber Flow-Vu chamber
174 demonstrated an equivalent profile of dose retention and delivery versus the reference chamber. The
175 Compact Space Chamber Plus (Medical Developments), the OptiChamber Diamond and

176 InspiraChamber devices all retained approximately twice as much drug, delivering around half the
177 dose and showing non-equivalent performance compared with the Aerochamber Flow-Vu chamber
178 and reference chamber (pre-treated AerochamberPlus chamber). Thus, the performance of VHCs
179 that resemble one another in terms of appearances and dimensions may differ markedly, implying
180 that VHCs should not automatically be considered interchangeable [39]. Although equivalent
181 performance between different VHCs has been demonstrated [40], a recent *in vitro* study [41] and a
182 literature review [42] provides further support for the results found by Dissanayake and coworkers
183 [39]. In considering the important attributes of such delivery devices, the review notes a shift in
184 emphasis from chamber size and shape to other aspects, such as consistency of drug delivery, static
185 charge reduction, valve performance, and factors optimizing facemask effectiveness, such as
186 flexibility and seal [42]. Since differences exist between different spacers or different VHCs, which
187 in some cases are sufficiently large that meaningful and overt clinical differences would be
188 anticipated as a result, each pMDI spacer/VHC combination should be treated as a unique inhaled
189 medication delivery system [29]. In this connection, the European Medicines Agency (EMA)
190 guidance recommends that the development and registration process for drug products delivered by
191 pMDIs includes testing and supporting *in vitro* and *in vivo* data of the pMDI when used with at least
192 one named spacer/VHC [43]. In addition, the EMA guidance states that asthma patients with well-
193 controlled disease by inhaled medications delivered through pMDIs plus spacer/VHC should
194 always use the same type of spacer/VHC and not switch to a different spacer/VHC that may deliver
195 different amounts of drugs [43].

196 The EU registration documentation for pMDIs (Summary of Product Characteristics and Patient
197 Information Leaflet) specifically note the VHC to be used should be based upon the device used in
198 the product development/registration studies. In case of a spacer/VHC substitution, appropriate
199 equivalency data for the alternative device must be presented [43]. Surprisingly, at variance with
200 EMA, other regulatory authorities, such as for instance the US Food and Drug Administration
201 (FDA), do not require data for a specific named spacer in order to support pMDI approval.

202 However, in a draft FDA Chemistry, Materials and Controls Industry guidance for orally inhaled
203 products issued in 1998 by the centre for Drug Evaluation and Research, there is recognition that
204 clinical efficacy assessment of pMDI delivered aerosols requires consideration of the presence of a
205 spacer/VHC [44]

206 In conclusion, there is published evidence that the union of a particular pMDI and a given
207 spacer/VHC is considered a specific inhaled medication delivery system. Therefore, we recommend
208 physicians to focus on selecting the most appropriate spacer/VHC for the patient and their pMDI(s),
209 given the weight of clinical evidence available. Although the non-interchangeability of VHCs is
210 recognized [40-42], we also recommend clinicians to monitor for any changes in disease control if
211 the patient's VHC was switched. Furthermore, we believe that pharmacists need to appreciate that
212 spacers/VHCs may deliver different amounts of drug from the pMDI and therefore substitution of a
213 different device from that prescribed by the physician may have an impact to the patient. Finally,
214 regulatory authorities need to be aware of the risks inherent in the current approval process of
215 spacers VHCs through CE mark registration and look for improvements to, at the very least, restrict
216 the ability of devices with serious design/quality flaws to be able to be approved and used by
217 patients.

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341

45. Table 1 Guidelines recommending spacer or valved holding chambers (VHCs)

Institution	year	Recommendation(s)
American Association of Respiratory Care	2007	A spacer/VHC should be used with an MDI; A spacer/VHC with facemask is appropriate for patients (usually < 3 years) unable to use a mouthpiece.
American College of Chest Physicians/American College of Allergy, Asthma & Immunology	2005	For patients who have trouble coordinating inhalation with device actuation, the use of a spacer (with a valve) may obviate this difficulty; The use of spacers is mandatory for infants and young children.
British Thoracic Society / Scottish Intercollegiate Guidelines Network	2012	Children and adults with mild and moderate exacerbations of asthma should be treated by bronchodilators given from a pMDI + spacer/VHC with doses titrated according to clinical response; In children aged 0-5, pMDI + spacer are the preferred method of delivery of β_2 agonists or inhaled steroids; The spacer should be compatible with the pMDI being used.
Canadian Pediatric Asthma Consensus Guidelines	2005	The use of a VHC with pMDI is strongly recommended for children
Canadian Thoracic Society	2010	The addition of a VHC with mouthpiece is helpful in overcoming poor hand-mouth coordination and reducing side effects, with increased drug delivery and lung deposition; VHCs with facemask attachments are useful for the elderly, who can use four to six tidal breaths for each actuation of the medicine.
Global Initiative on Asthma (GINA)	2017	pMDI + dedicated spacer/VHC with facemask is the preferred delivery system for children 4 years of age and younger; pMDI + dedicated spacer/VHC with mouthpiece is the preferred delivery system for children between 4 and 6 years of age.
Global Initiative for Chronic Obstructive Lung Disease (GOLD)	2014	For the MDI, the addition of a large or small volume spacer often overcomes coordination problems, and improves lower airway deposition and clinical benefit.
International Primary Care Respiratory Group	2006	The preferred device for administering inhaled asthma medication for infants and young children is a pMDI with a spacer and face mask; As the child's ability to co-operate improves (often around the age of 4-6 years), a spacer with a mouthpiece can be used rather than a face mask.
National Heart, Lung, and Blood Institute	2007	All patients taking inhaled steroids should use a spacer/VHC; Patients under 5 years should use a spacer/VHC with facemask for inhaled steroids.
Dutch College of General Practitioners (NHG) guidelines asthma and COPD	2014	Children: pMDIs should always be used in combination with a spacer/VHC Adults: pMDIs should always be used in combination with a spacer/VHC, unless the patient can use a pMDI

		adequately
National Institute for Clinical Excellence, (NICE, UK)	2010	Spacer/VHC recommended with a facemask where necessary for both corticosteroids and bronchodilators (children under 5); A pMDI used with an appropriate spacer/VHC is first choice for corticosteroids (children aged 5-15 years) For COPD patients, pMDI alone is rarely suitable for use with the elderly; The spacer should be compatible with the patient's pMDI.

342

343