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Salbutamol relative lung and systemic bioavailability of large and small spacers

Syed H. R. A. Mazhar and Henry Chrystyn

Abstract

Differences between the size and shape of spacers may affect the emitted dose and provide different effects when interchanged during routine use. Using a urinary pharmacokinetic method we have measured the relative lung and systemic bioavailability from urinary salbutamol excretion 30 min (USAL0.5) and 24 h (USAL24), respectively, after the inhalation of two 100-μg doses from a Ventolin Evohaler when used alone (MDI) and when attached to the Volumatic (VOL) or the Aerochamber Plus (AERO) spacers. The in-vitro properties of the emitted dose were determined. The mean (s.d.) USAL0.5 values following MDI, VOL and AERO (n = 13 volunteers) were 5.7 (1.9), 16.4 (8.2) and 14.8 (7.4) μg, respectively. VOL and AERO were significantly greater ($P < 0.001$ and < 0.01, respectively) than MDI. Comparison of VOL and AERO was similar with a mean ratio (90% confidence interval) of 108.2 (84.5, 138.6)%. USAL24 values between the three inhalation methods were similar. The values for the mean (s.d.) fine particle dose of two 100-μg doses emitted from MDI, VOL and AERO were 83.0 (6.8), 83.6 (4.6) and 73.6 (2.9) μg and the mass median aerodynamic diameters were 2.7 (0.03), 2.8 (0.07) and 2.9 (0.10) μm, respectively. The results showed that during routine use the Volumatic and the Aerochamber Plus spacers should provide similar lung and systemic delivery when attached to a Ventolin Evohaler.

Introduction

Large volume spacers, otherwise known as valved holding chambers, when attached to a metered-dose inhaler (MDI) solve problems patients have with co-ordination of dose release and inhalation as well as reducing the amount that impacts in the mouth and throat (Barry & O'Callaghan 2003). These add on devices improve lung deposition (Newman et al 1984, 1991) with a resultant increase in the degree of bronchodilation (Cushley et al 1983; Broeders et al 2003).

There are many different spacer devices available ranging from small to large volumes (750 mL), in different shapes. Some studies have shown a difference in response between spacers (Lindgren et al 1980; Lipworth & Clark 1998) whereas others have not (Lulling et al 1980; Newman et al 1991). However, due to the close proximity of the plateau of the dose–response curve when using standard spirometry tests (Newman et al 1991), induced bronchoconstriction followed by study dose administration is usually required (Fontana et al 1999). The latter method is not generally applicable to patients.

Dose emission and the aerodynamic characteristics of the emitted dose will have an effect on lung deposition (Barry & O'Callaghan 2003) and the resultant therapeutic and systemic effects. It has been shown that dose emission varies from one type of spacer to another (Barry & O'Callaghan 1996) when used with chlorofluorocarbon (CFC) and CFC-free propellant formulations (Dubus et al 2001). The majority of salbutamol MDIs now contain CFC-free propellants. Some of these CFC-free formulations include ethanol with a hydrofluoroalkane (HFA) propellant, which slows the speed of the emitted aerosol (Barry & O'Callaghan 1997) e.g. Airomir (TEVA, UK). The switch to CFC-free formulations of inhaled corticosteroids has not been easy, especially for beclometasone and budesonide. Further in-vitro studies have shown that there is a different dose emission from different spacers and for different drugs (Barry & O'Callaghan 1999).

Studies using plasma salbutamol as a surrogate marker of lung deposition have shown that Airomir provides a greater relative lung bioavailability than the CFC-based formulation (Clark & Lipworth 1996). When this MDI product was used with different types of spacer the

School of Pharmacy and Institute of Pharmaceutical Innovation, University of Bradford, Bradford, West Yorkshire, BD7 1DP, UK

Syed H. R. A. Mazhar, Henry Chrystyn

Division of Pharmacy and Pharmaceutical Sciences, School of Applied Sciences, University of Huddersfield, Huddersfield, West Yorkshire HD1 3DH, UK

Henry Chrystyn

Correspondence: Henry Chrystyn, Division of Pharmacy and Pharmaceutical Sciences, School of Applied Sciences, University of Huddersfield, Huddersfield HD1 3DH, UK.
E-mail: h.chrystyn@hud.ac.uk

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relative lung deposition from the Nebuhaler was greater than that of the Volumatic, which in turn was greater than the Aerochamber. There was no significant difference between the Aerochamber and the MDI used alone (Lipworth & Clark 1998). However, those last two studies used doses much higher than those used in routine practice and the effect of multiple actuations on the dose emission properties of these products is not known. Also the Airomir mouthpiece is not compatible with the Volumatic so the studies must have used an adapter. As well as this, Airomir includes ethanol in the formulation and Gabrio et al (1999) reported that ethanol decreases the velocity and increases the temperature of the emitted aerosol plume. The behaviour of other CFC-free formulations of salbutamol when attached to spacers cannot therefore be ascertained from the reports using Airomir.

There have been no studies comparing the lung deposition properties of Ventolin Evohaler (containing the new HFA-134a propellant) with different spacers although it is the most widely used CFC-free salbutamol MDI. When this product was reformulated with HFA propellants it was designed as a seamless transitional change when used alone and when attached to the Volumatic spacer (Cripps et al 2000). Since dose emission from spacers is dependent on the drug (Barry & O'Callaghan 1999), spacer (Barry & O'Callaghan 1996; Lipworth & Clark 1998; Dubus et al 2001) and the formulation (Kenyon et al 1995; Dubus et al 2001), we have compared the relative lung bioavailability of salbutamol when a Ventolin Evohaler was attached to a large and a small volume spacer. Using a urinary pharmacokinetic method (Hindle & Chrystyn 1992) we have determined the relative lung and systemic bioavailability following inhalation through a small and large volume spacer. This urinary pharmacokinetic method used the amount of salbutamol excreted in the first 30 min to identify the relative lung bioavailability, and the cumulative amount of salbutamol and its metabolite excreted over the 24 h post-inhalation to identify relative systemic bioavailability.

Materials and Methods

In-vivo study

Local Research Ethics Committee approval was obtained and all subjects gave signed informed consent. On separate study days healthy subjects inhaled two separate 100-μg doses of salbutamol from a Ventolin Evohaler (GlaxoSmithKline, UK) (MDI), the MDI attached to the Volumatic Spacer (GlaxoSmithKline, UK) (VOL) or the MDI attached to the adult version of the Aerochamber Plus (Trudell, Canada) (AERO). There was a period of seven days between each study dose administration and the order was randomized. All subjects were highly trained and competent with each method of inhalation. Each dose discharged from the MDI or into a spacer was inhaled using a slow vital capacity inhalation manoeuvre. Before dosing all spacers were washed (see 'Washing of spacers' below). Each single dose discharged into a spacer was inhaled within the first second of discharge into the spacer. Fifteen minutes pre-dosing all subjects voided their urine. Also, subjects abstained from caffeine beverages for the six hours before until 24 h after each study dose. Thirty minutes after the start of each study dose inhalation subjects provided a urine sample (USAL0.5). They then pooled all their urine over the next 24 h into a container stored at 4°C (USAL24). The pH and volume of each sample was recorded and samples were stored at −20°C before analysis. The pH values of the urine samples were all below pH 7, hence there was no variability due to passive tubular reabsorption (Hindle & Chrystyn 1992).

After inhalation of the two study doses each spacer was rinsed with water to collect the residual dose. Aqueous and urine samples were assayed for their salbutamol content using an extensive modification of the high-performance liquid chromatography (HPLC) assay reported by Hindle & Chrystyn (1992)—see 'HPLC assay' below. The 24-h urine samples were hydrolysed before HPLC assay, to determine the total amount of salbutamol and its metabolite (Hindle & Chrystyn 1992).

One-way analysis of variance with the application of Bonferroni correction was used to determine any difference between the urinary excretions from the inhalation methods. To identify equivalence of the urinary excretions between the inhalation methods, the USAL0.5 and USAL24 amounts for each inhalation method were log transformed. From the mean square error of the analysis of variance, using patients and inhalation method as the main factors, the mean ratio (90% confidence interval) was calculated.

In-vitro

The emitted dose from MDI, VOL or AERO was characterized using the Andersen Cascade Impactor (Copley Scientific Ltd, UK) operated at 28.3 L min^{-1} using a 4-L inhalation volume. The method is described in the British Pharmacopoeia (2005). Spacer preparation pre-dosing was in accordance with the washing procedure described in 'Washing of spacers' below and the dose was inhaled within 1 s of discharge into the spacer. These procedures were identical to those used for the in-vivo study. The emitted dose was that discharged ex-mouthpiece (TED), the throat deposited fraction was that deposited in the USP throat of the Andersen Cascade Impactor (ACI) plus stages S0 and S1, whilst the fine particle dose (FDP) was the amount deposited on stages 2 to the final filter (< 5.8 μm). The mass median aerodynamic diameter (MMAD) was the particle size corresponding to 50% of the dose deposited into the cascade impactor. For each inhalation method five separate determinations were made using two single 100-μg doses.

HPLC assay

Salbutamol was isolated from urine samples using Oasis HLB 30 mg mL^{-1} (Waters, UK) solid-phase extraction cartridges. These cartridges were pre-conditioned using 2 mL methanol followed by 45 mM potassium dihydrogen phosphate buffer (pH 7.0). After application of the sample, cartridges were washed with 15 mM potassium dihydrogen phosphate buffer (pH 7.0), followed by 5% methanol, 2% acetonitrile and finally 0.25% tetrahydrofuran. Salbutamol was removed from the cartridges using 2% acetic acid and evaporated to dryness using nitrogen. The analyte was then reconstituted with the HPLC mobile phase. To quantify the salbutamol ester sulphate metabolite, urine samples were boiled with 0.1 M hydrochloric acid before extraction.

The mobile phase was 10:8:14:68% v/v acetonitrile: tetrahydrofuran:methanol:buffer pumped at a flow rate of 1 mL min^{-1} through a Zorbax column (ODS 5 μm, 25 cm × 0.46 mm i.d., Phenomenex, UK) with a security guard cartridge (ODS, Phenomenex, UK). The buffer was 5 mM potassium dihydrogen phosphate adjusted to pH 2.5 with phosphoric acid and contained 25 mM sodium dodecyl sulphate. Fluorescence detection using an excitation of 269 nm and emission of 312 nm was used and terbutaline sulphate was the internal standard.

Aqueous salbutamol samples were assayed using the same HPLC method (without extraction). The salbutamol retention time was approximately 24 min and terbutaline eluted after 27 min. Calibration curves demonstrated linearity. The limit of detection for aqueous salbutamol samples and urine salbutamol and its metabolite was 2.0, 4.0 and 4.8 μg L^{-1}, respectively. Similar concentrations for the limit of quantification were 6.1, 12.1 and 14.6 μg L^{-1}.

Washing of spacers

For the in-vitro and in-vivo studies each spacer was washed before each procedure. They were washed in lukewarm mild detergent (equivalent to hand washing dishes), rinsed with water and left to air dry.

Results

The mean (s.d.) age and weight of the 13 (7 female) volunteers was 31.2 (7.6) years and 64.9 (10.8) kg. Each individual's USAL0.5 value is shown in Figure 1. Salbutamol urine concentrations after MDI, VOL and AERO ranged between 50.4–283.9, 55.3–649.9 and 200.0–441.1 μg L^{-1}, respectively. The in-vitro and in-vivo data are summarized in Table 1. USAL0.5 after VOL and AERO inhalations were both greater than MDI with respective mean differences (95% confidence interval) of 10.6 (4.2, 17.1; $P < 0.001$) and 9.1 (2.7, 15.5; $P < 0.01$) μg. USAL0.5 values following VOL and AERO were similar with a mean difference (95% confidence interval) of 1.5 (−7.9, 4.8) μg. There was no difference between the values of USAL24 for each inhalation method. The mean ratio (90% confidence interval) between VOL and AERO for USAL0.5 and USAL24 was 108.2 (84.5, 138.6)% and 121.8 (100.0, 145.9)%.

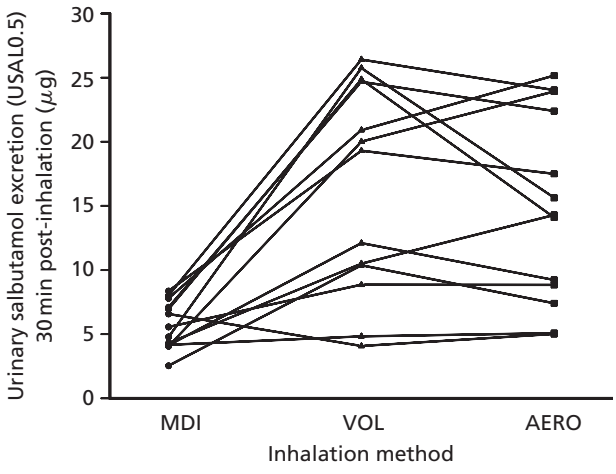

Figure 1 Amounts of salbutamol excreted by each individual in the first 30 min after the inhalation of two 100-μg doses of salbutamol using different inhalation methods (Ventolin Evohaler when used alone (MDI) and when attached to the Volumatic (VOL) or the Aerochamber Plus (AERO) spacer).

Table 1 In-vivo and in-vitro data from two 100-μg doses of salbutamol using different inhalation methods: Ventolin Evohaler when used alone (MDI) and when attached to the Volumatic (VOL) or the Aerochamber Plus (AERO) spacer

	MDI	VOL	AERO
ACI (in-vitro study): n = 10 single doses			
Spacer		74.9 (6.1)	90.6 (6.7)
TED	176.6 (7.6)	94.9 (4.6)	85.3 (4.5)
Throat	93.6 (7.4)	11.3 (1.9)	11.7 (1.2)
FDP	83.0 (6.8)	83.6 (4.6)	73.6 (2.9)
MMAD	2.69 (0.03)	2.76 (0.07)	2.91 (0.10)
Urinary salbutamol (in-vivo study): n = 13 volunteers			
USAL0.5	5.7 (1.9)	16.4 (8.2)	14.8 (7.6)
USAL24	100.2 (16.7)	97.3 (12.7)	84.6 (25.8)

Values are mean (s.d.). All values in μg except MMAD (mass median aerodynamic diameter) in μm. ACI, Andersen Cascade Impactor; FDP, fine particle dose; TED, dose discharged ex-mouthpiece.

Discussion

Regulatory limits for the bioequivalence of formulations are that the 90% confidence limits should be between 80–125% for C_{max} and AUC, whilst it has been suggested that when comparing relative potencies of inhaled products these limits should be between 0.67 and 1.50 (Parameswaran 1999). Application of these limits to the urinary salbutamol excretions in the first 30-min post-dose (USAL0.5) suggested that there was a trend for the relative lung deposition and sytemic delivery of salbutamol from a Ventolin Evohaler to be similar when it was attached to the Volumatic and the Aerochamber Plus. This cautious conclusion was made due to the small number of volunteers studied (13); much larger numbers of subjects may need to be studied to make firmer conclusions. This comment would apply for all studies that have been shown to suggest comparability between inhaled products. Most of the studies that were included in a meta-analysis comparing different inhalation methods (Brocklebank et al 2001) also used a low number of subjects, and were designed to show equivalence. We have shown that the urinary salbutamol pharmacokinetic method was more sensitive to detect a difference in relative lung deposition than the methacholine challenge method recommended by Regulatory Authorities (Tomlinson et al 2003). Furthermore, we studied volunteers and it may be that those with asthma may have different airway deposition. However, it has been shown that the only difference between

volunteers and those with asthma is that lung deposition is related to airway calibre (Lipworth & Clark 1997).

The larger relative bioavailability to the body (described by the USAL24 amounts) for the MDI method compared with that of the spacers was due to the larger emitted dose. Also, a larger proportion of the emitted dose will have been swallowed compared with when the MDI was attached to a spacer. The similar values for the 24-h urinary excretion for the two spacers suggested that the amounts swallowed following inhalation of these methods was similar.

When a dose is discharged into a spacer, impaction of the particles onto its walls will increase as the size of the spacer decreases. This is because the velocity effects of the emitted plume will be greater. This was confirmed by the smaller emitted dose from the Aerochamber (150-mL capacity) compared with the Volumatic (750 mL). Also, despite the minimal delay between dose discharge into the spacer and inhalation, the larger volume of the Volumatic would result in more evaporation of the aerosolized dose. This contributed to a smaller particle size. These all combined to provide a dose that was emitted from the Volumatic that had a higher fine particle dose and smaller MMAD compared with the Aerochamber. These in-vitro parameters translated to the observed small (but insignificant) differences in the relative lung and systemic bioavailability of the two spacers. This observation provided further evidence of in-vitro and in-vivo correlations in line with previous suggestions (Silkstone et al 2002a; Barry & O'Callaghan 2003). However, when this comparison was extended to the MDI alone with the spacers the link was not so clear. For example, the fine particle dose and MMAD of the MDI alone and the Volumatic were very similar yet the relative lung deposition was not. This highlighted the value of inhaling from a static cloud, which occurs when using a spacer, and suggested that comparisons that attempt to find a link between in-vitro and in-vivo data should consider the inhalation method and technique used. The higher emitted dose for the MDI compared with that of the spacers did translate into more drug being delivered to the systemic circulation (via the pulmonary and the gastrointestinal routes, with the latter predominating for the MDI).

The greater relative lung bioavailability of salbutamol for the MDI attached to a spacer compared with the MDI alone was consistent with previous reports of the corresponding CFC formulation attached to a spacer (Newman et al 1991; Silkstone et al 2002b). In contrast, Lipworth & Clark (1998) have shown that when using the Airomir MDI the relative lung deposition was greater when attached to a Volumatic compared with the Aerochamber, and that the latter was similar to the MDI used alone. This Airomir study did not present any in-vitro data to help understand the results and 12 doses were inhaled for each study dose. The effect of multiple dosing, each separated by 30 s, on the aerodynamics of the emitted dose was not addressed. The formulation of Airomir is different to that of the Ventolin Evohaler, the main difference being that Airomir contains 20% ethanol and so the emitted dose is slower and the aerosol is warmer than that of the Evohaler (Gabrio et al 1999). The difference in relative lung deposition between large and small spacers when using the Airomir (Lipworth & Clark 1998) compared with our contrasting results with the Ventolin Evohaler suggested that each CFC-free propellant formulation MDI product needs to be evaluated with different spacers before claims of interchangeability are made.

Conclusion

When it was anounced that the Volumatic Spacer was to be withdrawn there was so much concern that the decision was changed. This concern was due to the lack of any data comparing the two spacers when attached to a CFC-free salbutamol MDI. The results of this study have highlighted that a Ventolin Evohaler could be used with a Volumatic large volume spacer or an Aerochamber Plus without any difference in the relative lung and systemic delivery. This suggests that during routine use there should be no difference in the relative efficacy and safety if one of these spacers is substituted for the other when used with the Ventolin Evohaler. These results cannot be extrapolated to other inhalers and thus each formulation needs to be evaluated before a general claim of interchangeability can be made.

References

Barry, P. W., O'Callaghan, C. (1996) Inhalational drug delivery from seven different spacer devices. *Thorax* **51**: 835–840

Barry, P. W., O'Callaghan, C. (1997) In-vitro comparison of the amount of salbutamol available for inhalation from different formulations used with different spacer devices. *Eur. Respir. J.* **10**: 1345–1348

Barry, P. W., O'Callaghan, C. (1999) A comparative analysis of the particle size output of beclomethasone diproprionate, salmeterol xinafoate and fluticasone propionate metered dose inhalers used with Babyhaler, Volumatic and Aerochamber spacer devices. *Br. J. Clin. Pharmacol.* **47**: 357–360

Barry, P. W., O'Callaghan, C. (2003) The influence on inhaler selection on efficacy of asthma therapies. *Adv. Drug Deliv. Rev.* **55**: 879–923

British Pharmacopoeia (2005) Appendix XII F. Aerodynamic assessment of fine particles—fine particle dose and particle size distribution.

Brocklebank, D., Ram, F., Wright, J., Barry, P., Cates, C., Davies, L., Douglas, G., Muers, M., Smith, D., White, J. (2001) Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. *Health Technol. Assess.* **5**: 1–149

Broeders, M. E. A. C., Molema, J., Hop, W. C. J., Vermue, N. A., Folgering, H. T. M. (2003) Does the inhalation device affect the bronchodilatory dose reponse curve of salbutamol in asthma and chronic obstructive airways disease patients. *Eur. J. Clin. Pharmacol.* **59**: 449–455

Clark, D. J., Lipworth, B. J. (1996) Lung bioavailability of chlorofluorocarbon free, dry powder and chlorofluorocarbon containing formulations of salbutamol. *Br. J. Clin. Pharmacol.* **41**: 247–249

Cripps, A., Riebe, M., Schulze, M., Woodhouse, R. (2000) Pharmaceutical transition to non-CFC pressurised metered dose inhalers. *Respir. Med.* **94**: S3–S9

Cushley, M., Lewis, R., Tattersfield, A. (1983) A comparison of three techniques of inhalation on the airway response to terbutaline. *Thorax* **38**: 908–913

Dubus, J. C., Rhem, R., Dolovich, M. (2001) Delivery of HFA and CFC salbutamol from spacer devices used in infancy. *Int. J. Pharm.* **222**: 101–108

Fontana, G. A., Lavorini, F., Chiostri, M., Castellani, W., Boddi, V., Pistolesi, M. (1999) Large and small airway responses to procaterol hydrochloride administered through different extension devices in asthmatics. *J. Aerosol. Med*. **12**: 177–185

Gabrio, B. J., Stein, S. W., Velasquez, D. J. (1999) A new method to evaluate plume characteristics of hydrofluroalkane and chlorofluorocarbon metered dose inhalers. *Int. J. Pharm.* **186**: 3–12

Hindle, M., Chrystyn, H. (1992) Determination of the relative bioavailability of salbutamol to the lung following inhalation. *Br. J. Clin. Pharmacol*. **34**: 311–315

Kenyon, C. J., Dewsbury, N.J., Newman, S. P. (1995) Differences in aerodynamic particle size distributions of innovator and generic beclomethasone diproprionate aerosols used with and without a large volume spacer. *Thorax* **50**: 846–850

Lindgren, S. B., Formgren, H., Moren, F. (1980) Improved aerosol therapy of asthma: effect of actuator tube size on drug availability. *Eur. J. Respir. Dis*. **61**: 56–61

Lipworth, B. J., Clark, D. J. (1997) Effects of airway calibre on the lung delivery of nebulised salbutamol. *Thorax* **52**: 1036–1039

Lipworth, B. J., Clark, D. J. (1998) Early lung absorption profile of non-CFC salbutamol via small and large volume plastic spacer devices. *Br. J. Clin. Pharmacol*. **46**: 45–48

Lulling, J., Delwiche, J. P., Hidinger, K. G., Prignot, J. (1980) Influence of different extension-actuator tubes on the bronchodilation effect of a terbutaline sulphate aerosol. *Eur. J. Respir. Dis*. **61**: 56–61

Newman, S., Millar, A., Lennard Jones, T., Moren, F., Clarke, S. W. (1984) Improvement of pressurised aerosol deposition with Nebuhaler spacer device. *Thorax* **39**: 935–941

Newman, S. P., Talaee, N., Clarke, S. W. (1991) Salbutamol aerosol delivery in man with a Rondo spacer. *Acta. Ther*. **17**: 49–50

Parameswaran, K. N. (1999) Concept of establishing clinical bioequivalence of chlorofluorocarcbon and hydrofluoroalkane β-agonists. *J. Allergy Clin. Immunol*. **104**: S243–S245

Silkstone, V. L., Dennis, J. H., Pieron, C. A., Chrystyn, H. (2002a) An investigation of in vivo/in vitro correlations for salbutamol nebulized by eight systems. *J. Aerosol Med*. **15**: 251–259

Silkstone, V. L., Corlett, S. A., Chrystyn, H. (2002b) Relative lung and systemic bioavailability following inhalation from a metered dose inhaler compared with a metered dose inhaler attached to a large volume plastic spacer and a jet nebuliser. *Eur. J. Clin. Pharmacol.* **57**: 781–786

Tomlinson, H. S., Corlett, S. A., Allen, M. B., Chrystyn, H. (2003) Dose response relationships of urinary salbutamol excretion following inhalation. *Br. J. Clin. Pharmacol.* **56**: 225–227