Volumatic usage: some generic salbutamol metered dose inhalers can be used

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Abstract

Background – The 30 minute and 24 hour post-inhalation urinary excretion of salbutamol represents the relative amount of drug deposited in the lungs and total systemic absorption, respectively. Using this method two metered dose inhalers used with a Volumatic (Allen and Hanburys Ltd, UK) large volume spacer have been compared.

Method – Eleven healthy volunteers inhaled $4 \times 100 \mu\text{g}$ salbutamol from either a generic salbutamol (Baker Norton, UK) or Ventolin (Allen and Hanburys Ltd, UK) metered dose inhaler with a Volumatic. The order of administration was randomised with a seven day washout period. Urine samples were collected for 0–30 minutes and then pooled up to 24 hours after inhalation.

Results – The mean (SD) urinary salbutamol excretion 30 minutes after inhalation with the metered dose inhalers used with the Volumatic was 22.22 (4.63) and 21.30 (5.91) μg for the Baker Norton and Ventolin respectively, with a mean difference (95% confidence interval (CI)) of 0.92 (–0.65 to 2.49) μg . Similar amounts were excreted up to 24 hours after the dose with a mean (SD) urinary excretion of 116.1 (24.3) μg and 114.8 (22.3) μg , respectively, and a mean difference (95% CI) of 1.22 (–20.39 to 22.84) μg .

Conclusion – Inhalations from generic salbutamol (Baker Norton) and Ventolin metered dose inhalers with a Volumatic inhalation aid deliver similar amounts of drug to the lungs and the total systemic absorption from the two products is the same.

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A recent report has highlighted the different inhalation devices for the inhaled products that are available and the need for a generic spacer.¹ The suitability of any generic metered dose inhaler (MDI) with a Volumatic (Allen and Hanburys Ltd, UK) spacer device has been disputed.^{2,3} Although it is accepted that mouth-piece compatibility of generic inhalers does not guarantee clinical efficacy, much of the debate has centred on claims of in vitro deposition and on issues of spray kinetics. An intra- and interindividual variability within clinical subjects of the amount deposited in the lungs following inhalation would occur because of the

inhalation technique⁴ and variability of dosage delivery from MDI canisters,^{5,6} together with the calibre and size of airways. All these would influence the overall pharmacodynamic response. Clinical studies should be carried out to compare MDIs and demonstrate bioequivalence between inhaled products, but these may not be proven without some simultaneous measurement of the amount of drug deposited in the lung.

We have described a method of measuring the relative bioavailability of salbutamol to the lungs following inhalation. This index of pulmonary deposition is obtained from the amount of salbutamol excreted in the urine during the first 30 minutes after inhalation and represents the amount of drug that is renally excreted following absorption into the body via the lungs.⁷ The amount of salbutamol and its metabolite (the sulphate ester conjugate) excreted in the urine in the first 24 hours has been shown to represent an index of the systemic absorption of salbutamol following inhalation.⁷ This method has now been used to compare two MDI products when they are used with a Volumatic inhalation aid.

Method

Eleven healthy volunteers inhaled $4 \times 100 \mu\text{g}$ doses from a Ventolin (Allen and Hanburys Ltd, UK) or generic salbutamol (Baker Norton, Norton Healthcare Ltd, UK) MDI on separate study days. The Volumatic was used with each MDI and inhalation techniques were standardised according to the Volumatic patient information leaflet. On each occasion there were four separate actuations each followed by an inhalation. The MDI inhalation order was randomised and there was a seven day washout period between the two study days. All volunteers were highly trained in the inhalation technique used and experienced with this type of study. No volunteer had an upper respiratory tract infection during or in the four days preceding each of the study days. Urine samples were collected for 0–30 minutes and then pooled up to 24 hours after inhalation and salbutamol concentrations were measured.⁷ A paired Student's *t* test was used to compare differences and the mean difference and ratios together with their 95% confidence intervals (95% CI) were calculated.

Results

The mean (SD) age and weight of the 11 volunteers (four women) was 29.8 (8.5) years and 73.6 (16.6) kg, respectively. The pH of all

Individual with mean (SD) amounts of urinary salbutamol excreted in the first 30 minutes after inhalation using a Volumatic fitted with either a Ventolin or generic (Baker Norton) metered dose inhaler.

urine samples was between 4 and 6.5 so there was no renal excretion variability.⁷ The amount of salbutamol (in µg) excreted in the urine during the first 30 minutes by each individual following inhalation using a Volumatic with the Ventolin and generic (Baker Norton) MDI is shown in the figure. The respective mean (SD) was 21.30 (5.91) and 22.22 (4.63) µg with a mean difference (95% CI) of 0.92 (−0.65 to 2.49) µg. The mean (95% CI) ratio was 108.1 (98.0 to 114.2)% with an interindividual coefficient of variation of 11.28%. The mean (SD) 0–24 hour urinary excretion of salbutamol and its metabolite was 114.8 (22.3) and 116.1 (24.3) µg, respectively, with a mean difference (95% CI) of 1.22 (−20.39 to 22.84) µg. Expressed as a percentage of the inhaled dose the mean (SD) total amounts excreted in the urine are 28.7 (5.6)% and 29.0 (6.1)%, respectively.

Discussion

The total systemic absorption using each inhaler with the Volumatic is lower than that reported when the MDI was used on its own.⁴⁷ This is consistent with a previous study using the urinary excretion method⁸ which showed that this reduction was due to a decrease in the swallowed fraction following inhalation with the aid of a large volume spacer.

Bioequivalence of inhaled products can be assured if the amount of drug deposited onto the therapeutically active sites of the lungs following inhalation is the same.⁹ Although methods are available to split the amount of drug deposited into central and peripheral regions following inhalation from a modified canister,¹⁰ there is no conclusive evidence to suggest that deposition in different areas of the lung produces an altered pharmacodynamic response. A study has shown that the site of deposition in the lungs is not important for the bronchodilator effect of terbutaline,¹¹ but more

extensive research on this issue is required.

Although the urinary excretion method is an indirect method which indicates total lung dose rather than regional pulmonary deposition, it does allow a non-invasive comparison of relative lung bioavailability between two “off the shelf” salbutamol inhaler products within the clinical environment. Equal urinary excretions following inhalation from two salbutamol products goes some way to suggesting that they have similar in vivo behaviour. Comparable relative lung bioavailabilities coupled with in vitro depositions which indicate similar particle size distributions and dosage delivery suggests that, when using a consistent inhalation technique in the absence of airway variability, the drug should be deposited onto similar sites in the lungs.

The lack of a statistically significant difference between the MDIs when each was used with a Volumatic and the 95% confidence intervals of the ratio within the standard 80–120% limits show that the in vivo respirable fraction from the Volumatic is the same for the two inhalers. Although clinical subjects were not used in this study, we were able to use highly trained volunteers who are experienced with this type of study so variability in inhalation technique and airway calibre would be negligible. The use of four inhaled doses would also limit variability due to uneven dosage delivery from each spray.⁵ A recent report has revealed a difference in the in vitro dosage delivery of a range of generic MDIs.⁶ The observation that a generic salbutamol MDI can be used with a Volumatic spacer device can only be made, therefore, for the one used in this study or others with the same Product Licence.

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