

## Relative bioavailability of salbutamol to the lung following inhalation via a novel dry powder inhaler and a standard metered dose inhaler

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**Aims** The number of dry powder inhaler (DPI) devices could increase because they are easier to use than a metered dose inhaler (MDI). Using urinary excretion, the relative bioavailability of salbutamol to the lungs and the body for a prototype DPI has been compared with an MDI.

**Methods** A randomized, double-blind, two way crossover study compared the amount of salbutamol in the urine 30 min following inhalation of  $2 \times 100 \mu\text{g}$  salbutamol from a prototype DPI (Innovata Biomed Ltd, UK) and a Ventolin<sup>®</sup> (Allen and Hanburys Ltd, UK) MDI in 10 volunteers. The amount of salbutamol and its metabolite, the ester sulphate conjugate, renally excreted up to 24 h post inhalation was also determined to evaluate the relative bioavailability of salbutamol to the body.

**Results** The mean (s.d.) 30 min post-treatment urinary excretion for the prototype DPI and MDI was 8.4 (2.6) and 5.0 (1.9)  $\mu\text{g}$ , respectively ( $P < 0.001$ ). The total amount of salbutamol and its ester metabolite excreted in the urine over the 24 h period after inhalation was 187.9 (77.6) and 137.6 (40.0)  $\mu\text{g}$  ( $P < 0.05$ ).

**Conclusions** The prototype DPI delivered more salbutamol to the body and the lungs than a conventional MDI. This finding supports further development of the prototype DPI. The urinary salbutamol method is able to discriminate between two different inhalation systems.

**Keywords:** salbutamol, dry powder inhaler, metred dose inhaler

### Introduction

Considerable attention is now focused on the development of dry powder inhalers (DPI) [1], partially as a result of the phase-out of the chlorofluorocarbon (CFC) propellants traditionally used in metered dose inhalers (MDIs). DPIs offer other advantages over MDIs, for example, patients do not need to co-ordinate their inspiratory effort with actuation of the devices and are therefore easier to use. A novel multidose DPI has been developed (Innovata Biomed Ltd, UK) which contains a bulk drug reservoir and metering cone, to prevent double dosing. The DPI delivers 200 doses ( $100 \mu\text{g}$  salbutamol plus  $2.9 \text{ mg}$  lactose per dose) and incorporates a dose counter.

A simple, non-invasive technique exists for the evaluation of the relative bioavailability of salbutamol to the lung, which is based on the renal clearance of salbutamol and its metabolites [2]. The urinary recovery of unmetabolized salbutamol in the first 30 min post-treatment for two inhaled products is indicative of the relative bioavailability of salbutamol to the lung. Measurement of the 24 h urinary recovery of salbutamol and its sulphate conjugate metabolite allows an estimate of the relative systemic availability of the inhaled dose [2]. This technique has been shown to be sufficiently sensitive to discriminate between different inhaler

devices both with and without spacers [3, 4], different inhalation manoeuvres [5], formulations with different *in vitro* particle size distributions [6] and different doses of salbutamol [7].

In the present study, the technique was employed to compare the relative bioavailability of a standard dose of salbutamol to the lung administered via a prototype of the novel DPI (Innovata Biomed Ltd) and the innovator MDI (Allen and Hanburys Ltd).

### Methods

Ten healthy subjects (aged  $\geq 18$  years), who were thoroughly trained with inhalation techniques, gave written informed consent to participate. The study was approved by the Ethics Committee of the University of Bradford. Each subject undertook two 24 h study periods, which were separated by at least 6 full days. At the start of each period, subjects inhaled  $2 \times 100 \mu\text{g}$  salbutamol (nominal dose  $200 \mu\text{g}$ ). Each dose was separated by 30 s. Salbutamol was administered via Ventolin<sup>®</sup> MDI (Allen and Hanburys Ltd) [VEN-MDI] or a prototype DPI (Innovata Biomed Ltd) [IB-DPI] in a randomized, double-blind (double dummy), two-way cross over design. Both inhalers delivered a nominal dose of  $100 \mu\text{g}$  per actuation.

Subjects emptied their bladders immediately before drug administration and then urine samples were collected at 30 min and subsequently pooled until 24 h after the inhaled

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doses. The volume of urine passed was recorded and samples were stored at  $-20^{\circ}\text{C}$  before analysis. A previously validated, sensitive high performance liquid chromatography (h.p.l.c.) method was used to measure urine concentrations of salbutamol and its metabolite, the sulphate ester conjugate [2]. All amounts excreted in the urine are those for the free base. To account for any differences in the emitted dose, the amount of salbutamol excreted in each individual's urine over the first 30 min was divided by the total amount of salbutamol and its metabolites eliminated (in the urine) over the 24 h period post inhalation. The individual ratios for IB-DPI were divided by the corresponding VEN-MDI ratios and from these the mean (ratio) and its 95% confidence interval was calculated.

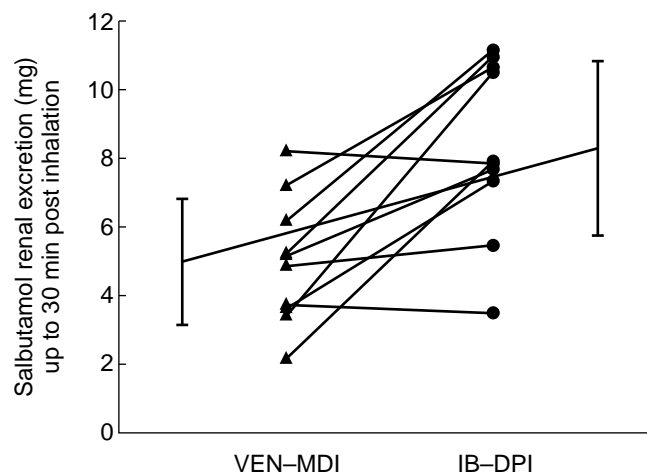
Subjects did not drink alcohol or caffeine-containing beverages for 12 h before or 24 h after treatment. Vital signs (heart rate and blood pressure) were recorded pre-treatment and at 5, 10, 15, 30 and 60 min post-treatment. Adverse events experienced by the subjects were recorded.

Statistical comparisons were made using analysis of variance.

## Results

Ten healthy subjects (five male and five female) with mean (s.d.) age, weight and height of 28.1 (8.5) years, 68.9 (13.4) kg and 172 (15) cm, completed the study. One subject received medication during the study (oral contraceptive). Healthy volunteers were used in this study to limit the variability from inhalation technique and differences in airway calibre.

Figure 1 shows that the amount of salbutamol recovered at 30 min post-treatment was significantly higher ( $P < 0.001$ ) after inhalation from IB-DPI compared with VEN-MDI. The mean (s.d.) amount of salbutamol renally excreted in the first 30 min following inhalation was 8.4 (2.6) and 5.0 (1.9)  $\mu\text{g}$  respectively, with a mean difference (95% confidence interval) of 3.4 (1.5, 5.3)  $\mu\text{g}$ . The mean (s.d.) amount of unmetabolized plus metabolized salbutamol recovered up to 24 h post-treatment was 187.9 (77.6)  $\mu\text{g}$  following inhalation using IB-DPI and 137.6 (40.0)  $\mu\text{g}$



**Figure 1** Mean (s.d.) and individual salbutamol renal excretion ( $\mu\text{g}$ ) up to 30 min post inhalation of  $2 \times 100 \mu\text{g}$  salbutamol via IB-DPI or VEN-MDI.

following inhalation using VEN-MDI ( $P < 0.05$ ), with a mean difference (95% confidence interval) of 50.3 (3.2, 97.4)  $\mu\text{g}$ .

The amount of drug recovered at 30 min expressed as a proportion of the total recovered up to 24 h post-treatment tended to be higher for the IB-DPI compared with VEN-MDI ( $4.8 \pm 1.9\%$  vs  $3.7 \pm 1.1\%$ ,  $P = 0.08$ ). The mean ratio (95% confidence interval) of these proportions for DPI:MDI was 1.41 (0.93, 1.90).

Following treatment with IB-DPI or VEN-MDI there were no significant changes in heart rate and systolic/diastolic blood pressure. Three subjects reported adverse events. One subject reported two incidences of tremor (mild to moderate) and two subjects reported one incidence of tremor (mild), all of which resolved after a maximum of 30 min. Three incidences of tremor were reported after use of IB-DPI and one after use of VEN-MDI.

## Discussion

The amount of salbutamol delivered to the lung is directly related to the amount of salbutamol recovered in the urine at 30 min post-treatment [2]. Thus, since the amount of unmetabolized drug recovered at this time was significantly higher following use of IB-DPI than VEN-MDI, then it follows that the amount of salbutamol delivered to the lung, in healthy volunteers, appeared higher following the use of IB-DPI than VEN-MDI under the conditions employed in this study. The total amount of salbutamol delivered to the body by each inhaler (either inhaled or ingested by the subject), as indicated by the total amount of unmetabolized plus metabolized salbutamol recovered in the urine up to 24 h post-treatment, was also higher following use of IB-DPI than VEN-MDI. The difference may be due to different amounts leaving the device when used *in vivo*. In order to take into account the apparent higher total dose delivered to each subject from the prototype IB-DPI, the ratio of the total dose delivered to the lung was calculated by dividing each individual 30 min urinary salbutamol excretion by the total amount of salbutamol and metabolites excreted in the urine over the 24 h period post inhalation. This proportion tended to be higher for IB-DPI compared with VEN-MDI indicating that the IB-DPI may be a better device to deliver salbutamol to the lungs than the conventional VEN-MDI. These results support further development of the prototype IB-DPI as an alternative to the VEN-MDI for delivery of inhaled salbutamol.

This study further validates the methodology for the determination of the relative lung bioavailability of salbutamol based on the analysis of urinary drug levels. The technique was able to discriminate between two different drug delivery systems. It is recognised that such a technique is a valuable tool for the development of new bronchodilator delivery systems in view of the relative insensitivity of widely used pharmacodynamic endpoints such as spirometry [8].

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