

# In vitro assessment of drug delivery through an endotracheal tube using a dry powder inhaler delivery system

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## Abstract

**Background** – Jet nebulisers and metered dose inhalers are widely used to deliver aerosolised drugs to the lungs of intubated patients in adult intensive care units. Drug delivery using these systems has been shown to be inefficient and both forms of delivery have the potential to induce paradoxical bronchoconstriction in patients with reactive airways disease.

**Methods** – Experiments were carried out to determine whether it was possible to deliver drug from a dry powder delivery system through an endotracheal tube. A 200 µg budesonide Turbohaler was enclosed in a chamber which allowed it to be inserted into a ventilator circuit. Experiments were performed with a multistage liquid impinger in which drug was drawn through the Turbohaler and endotracheal tube at 60 l/min providing an index of the maximum drug delivery achievable via this route. A second series of experiments was performed in which the Turbohaler was placed in a ventilator circuit using a Servo 900C volume cycled ventilator. Drug delivered from the Turbohaler during the inspiratory phase was collected on a filter placed between the end of a 9 mm endotracheal tube and a model lung. A tidal volume of 500 ml and inspiratory time of 0.5 seconds was used. Budesonide was assayed using an ultraviolet spectrophotometric assay.

**Results** – Thirty percent of the nominal dose passed through the endotracheal tube and was collected in the multistage liquid impinger. Mean drug delivery to the filter in the ventilator circuit was 20%.

**Conclusions** – This in vitro study indicates that drugs from dry powder inhalers (in this case the Turbohaler) can be satisfactorily delivered through endotracheal tubes and that clinical evaluation of this technique is now indicated.

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Keywords: aerosol, endotracheal tube, dry powder inhaler.

Jet nebulisers have traditionally been used in adult intensive care units when administering drugs via endotracheal tubes to the lower airways of intubated patients.<sup>1-4</sup> More recently, many centres – particularly in North America – have been using metered dose inhalers for

this purpose.<sup>3,5-9</sup> It has been known for some time that the effective drug delivery from conventional jet nebulisers is generally low due to factors such as raining out of drug in the ventilator,<sup>1-4</sup> while other problems such as cooling of the inspired air, adding gas volume to the ventilator circuit, and poor reproducibility of output have been cited as reasons for considering alternative systems.<sup>5,7,10</sup> Both dosimetric jet nebulisers, which deliver drug only during inspiration,<sup>11</sup> and ultrasonic nebulisers<sup>12</sup> have been shown in in vitro studies to be capable of delivering significantly greater doses, but they have not been widely accepted and no deposition studies have been performed to confirm their promise. Comparisons of metered dose inhaler and jet nebuliser based systems in the intensive care setting have produced conflicting results, with some indicating improved drug delivery using metered dose inhaler systems<sup>7</sup> and some improved delivery with jet nebulisers.<sup>13</sup> Reviewing the evidence, it would appear that both metered dose inhaler and jet nebuliser systems, if suitably chosen and used optimally, can deliver therapeutic doses to the lungs of intubated patients, and that the main impetus in North America to move towards the metered dose inhaler based systems is the financial saving, principally in respiratory technologist time, that such systems provide.<sup>5,6,8</sup>

One problem common to aerosols generated by both wet nebuliser and metered dose inhaler systems is the ability of the aerosol to induce bronchoconstriction in those with obstructive airways disease.<sup>14,15</sup> The potential for inducing such events in some severely ill asthmatic patients in the intensive care setting is of some concern.

A series of in vitro experiments was performed to determine whether it is possible to deliver budesonide, in the form of a dry powder, via endotracheal tubes using a Turbohaler and a novel adapter for use in ventilator circuits.

## Methods

Budesonide Turbohalers, 200 µg, were used for these experiments. The standard Turbohaler mouthpiece was modified by cutting back the outer covering to reveal the inner cylinder containing the spiral disaggregation channels, which could then be inserted into the end of an endotracheal tube. The Turbohaler was enclosed in a chamber or "spaceship" (Astra Draco, Lund, Sweden) which permits air to flow through the Turbohaler and out via the

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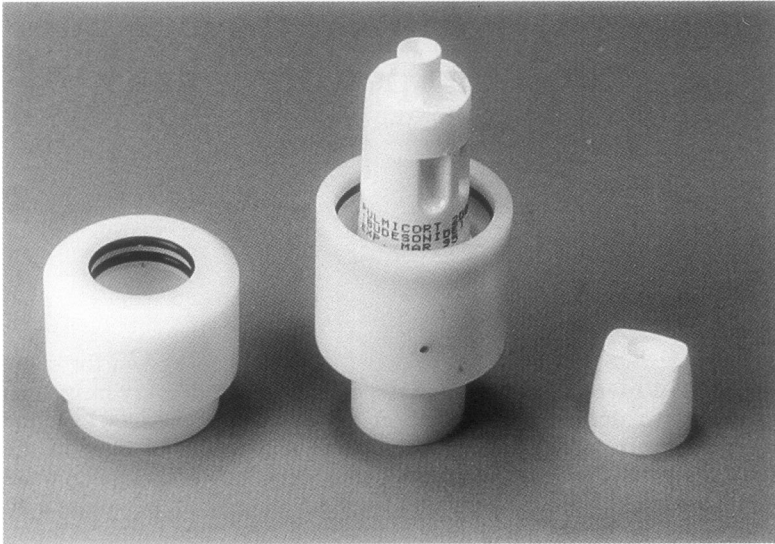


Figure 1 Turbohaler with modified mouthpiece and "spaceship".

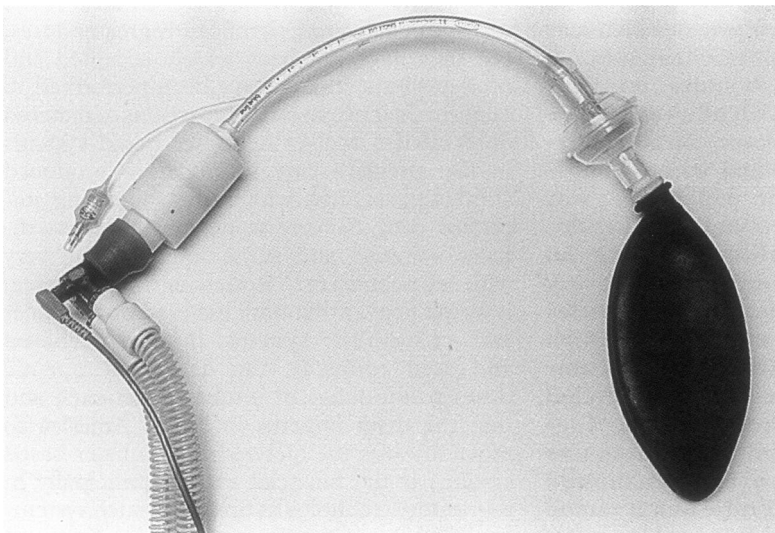


Figure 2 Positioning of the Turbohaler within a ventilator circuit between the manifold and the endotracheal tube.



Figure 3 Pattern of powder deposition at the proximal end of the endotracheal tube after multiple actuations from the Turbohaler.

mouthpiece (fig 1). The "spaceship" permits loading of the dosing channels without removing it from the device. Uncut 32 cm straight endotracheal tubes (Portex, Hythe, UK) with an internal diameter of 9 mm were used for all the experiments.

Initial experiments ( $n=6$ ) were performed in which an Astra multistage liquid impinger (Copley, Nottingham, UK) was used to assess both the quantity of drug and particle size distribution of the drug particles. The Turbohaler with the endotracheal tube attached was inserted into the inlet of the multistage liquid impinger and air was drawn through the system at a rate of 60 l/min. When inflated, the endotracheal tube cuff provided a good seal when inserted into the inlet of the multistage liquid impinger, ensuring that the entire air flow (60 l/min) passed through the Turbohaler. The location of particle deposition is determined by the aerodynamic size of the particle. Those depositing on stages 3 and 4 represent particles of  $<6.8 \mu\text{m}$  in diameter and are often arbitrarily referred to as being in the "respirable range".

Ten actuations were used for each experiment to ensure detectable quantities of drug on each stage of the multistage liquid impinger. Each stage was washed with 50 ml of ethanol and the amount of budesonide deposited was measured using spectrophotometer ( $\lambda=243 \text{ nm}$ ). The results were compared with results from a standard 200  $\mu\text{g}$  Turbohaler measured in the same way.

Further experiments ( $n=15$ ) were then performed with the Turbohaler placed in a ventilator circuit between the manifold and endotracheal tube as shown in fig 2. Drug delivered via the endotracheal tube was collected on a filter (Kendall Curity anaesthesia filters) placed between the end of the tube and a model lung. A Servo 900C (Siemens, Sweden) ventilator was used with the tidal volume set at 500 ml and an inspiratory time of 0.5 seconds. A total of ten actuations were used for each experiment to ensure adequate quantities of drug on the filter. The pause button on the ventilator permits the Turbohaler to be loaded between inspiratory flows and potentially allows a pause for breath holding at the end of inspiration.

Each filter was washed with 100 ml of ethanol and the budesonide was measured using a spectrophotometric method.

## Results

The mean (SD) total dose from the standard Turbohaler including that retained on the mouthpiece was 204.1 (19.6)  $\mu\text{g}$ . The dose collected by the multistage liquid impinger was 142.6 (16.4)  $\mu\text{g}$  and the dose of particles  $<6.8 \mu\text{m}$  in diameter was 91.2 (8.9)  $\mu\text{g}$ . With the endotracheal tube attached, the mean (SD) quantity of drug delivered to the multistage liquid impinger was 60.4 (4.8)  $\mu\text{g}$  per actuation and the dose of particles  $<6.8 \mu\text{m}$  in diameter was 46.8 (3.2)  $\mu\text{g}$ . The total dose of drug delivered to the filter at the distal end of the

endotracheal tube when included in the ventilator circuit was 41.1 (3.7) µg per actuation.

Figure 3 illustrates the pattern of powder deposition at the proximal end of the endotracheal tube following multiple actuations, illustrating that the powder continues to spiral after leaving the mouthpiece.

### Discussion

These results suggest that drug from dry powder delivery systems can be delivered efficiently via endotracheal tubes and that such systems may be valuable in the intensive care setting. Results with the multistage liquid impinger indicate that as much as 30% of the nominal dose can be delivered via an endotracheal tube. Although the total dose on stages 3 and 4 is reduced compared with the standard Turbohaler, these results also suggest that the tubing is particle selective in that the ratio of drug on stages (3 + 4) to (1 + 2) increases from 1.77 to 1 to 3.4 to 1 when delivered via the tube.

Air flow through the Turbohaler in the multistage liquid impinger experiments is essentially a square wave with flow reaching 60 l/min very rapidly which may not be the case in a ventilator circuit. Using an arbitrary tidal volume of 500 ml, delivery to the filter of 20% was still achieved in the ventilator filter study. Deposition studies assessing drug delivery from jet nebuliser and metered dose inhaler systems have found that the lung dose for intubated patients is generally in the range 1–6%.<sup>14,7</sup> It has recently been shown in vitro that the use of tubing to effectively extend the actuator beyond the tip of the endotracheal tube can deliver doses approaching 100% to the lower respiratory tract.<sup>16</sup> Unfortunately much of the aerosol is likely to impact directly on respiratory epithelium just beyond the endotracheal tube, and damage to the epithelium is likely to occur due to the impaction of high concentrations of propellants and surfactants such as oleic acid.<sup>17</sup>

Previous work has found that in vitro studies have overestimated lung doses from both metered dose inhaler<sup>6,10</sup> and nebuliser<sup>4</sup> based systems. It is likely that these experiments also overestimate the dose that would be delivered if this powder based system was used with intubated patients, particularly as there are a number of potential problems that should be considered. The gases in the ventilator circuit were not humidified in these experiments and the use of humidification might reduce drug delivery as it does for jet nebulisers.<sup>18</sup> Furthermore, clean dry endotracheal tubes were used. From fig 3 it is evident that the powder

continues to spiral along the inner surface of the tube for several centimetres and, if this surface was wet, increased drug loss is likely. Beyond this the powder is presumably re-entrained into the air flow, so it is important to use a clean dry extension to connect the mouthpiece to the endotracheal tube and to use non-humidified gases during the administration of the aerosol.

The system we describe is easy to use and our initial results indicate that relatively efficient drug delivery is possible using a dry powder delivery system. We would suggest that this system is worthy of further assessment in the clinical setting and may prove to be a useful addition to drug delivery systems in the intensive care unit.

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