An alternative aerosol delivery system for amiloride

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Background – The advent of novel treatments such as aerosolized amiloride are potentially useful additions to the therapeutic options available for the treatment of cystic fibrosis. Unfortunately, amiloride and other aerosolized drugs such as antibiotics are generally administered via jet nebulisers which are time consuming to use, and thus limit the acceptance and efficacy of these forms of treatment. In vitro experiments were performed in order to determine whether amiloride could be administered in dry powder form using a Turbohaler.

Methods – Amiloride was micronised and loaded into 200 µg Turbohalers. The dose delivered per actuation and particle size distribution of the generated aerosol were assessed using a flow of 60 l/min through the Turbohaler. The dose of amiloride delivered was measured by collecting the aerosol on a filter and the quantity of drug was assayed by an ultraviolet spectrophotometric method. The particle size distribution was assessed using a Malvern MasterSizer laser particle sizer and compared with that generated by a commercially available 200 µg budesonide Turbohaler.

Results – The mean (SD) dose delivered per actuation was 246.3 (40.4) µg. The volume median diameter of the amiloride aerosol was 3.80 (0.68) µm compared with 3.07 (1.47) µm for budesonide.

Conclusions – These results suggest that therapeutic doses of micronised amiloride could be delivered effectively and conveniently as a dry powder aerosol using a Turbohaler.

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The principal attraction of delivering drugs as aerosols for the treatment of pulmonary disease is that the drugs are delivered directly to the site of action, thus reducing the possibility of systemic side effects and permitting the use of drugs that are poorly absorbed by the gastrointestinal tract or extensively metabolised by the liver. There are, however, a number of disadvantages with this route of administration, including the high variability in dose delivered to the lungs and the inconvenience of relatively long treatment times associated with the use of jet nebulisers. For patients with cystic fibrosis, who may need to administer several drugs daily

via this route, the time consuming nature of nebuliser therapy is a major problem¹ and may be an impediment to good compliance. The list of drugs delivered as aerosols that may be of benefit in patients with cystic fibrosis is continually growing. In addition to bronchodilators and nebulised antibiotics, novel therapies such as amiloride²⁻⁴ and DNase^{5,6} are also currently delivered via jet nebulisers. Multicentre clinical trials are under way using nebulised amiloride⁴ and further studies are investigating the possible benefits of administering amiloride with inhaled uridine 5-triphosphate (UTP).⁷ However, because of its short duration of action⁸ it is currently administered at least four times per day,^{3,4} and hence any potential benefits are likely to be lost in many patients due to poor compliance.

It has previously been shown that micronised gentamicin could be administered as a dry powder aerosol using a Rotahaler,⁹ a much more convenient form of administration than a jet nebuliser. The availability of such a formulation for inhaled antibiotics would be welcomed by patients since treatment times would be reduced. This principle of using powder inhalers could be applied not only to currently used medication, but also to novel therapies such as amiloride. Dry powder inhalers are not only more convenient but there is also evidence that certain powder inhalers such as the Turbohaler (Astra Draco, Lund, Sweden) are more efficient than most jet nebulisers, providing adequate inspiratory flows can be generated.

A series of in vitro experiments was carried out in order to determine whether therapeutic doses of amiloride might be delivered quickly and conveniently using a Turbohaler.

Methods

Amiloride hydrochloride powder (5 g) was micronised using a Chrispro microniser (Chrispro Ltd, Canterbury, Kent, UK) at a mill pressure of 689.4 kPa and feed pressure of 206.8 kPa. Empty 200 µg Turbohalers were filled with 100 mg of the micronised amiloride. Experiments were carried out to assess particle size distribution and dose delivered using a "spaceship" (Astra Draco, Sweden). This simple device encloses the Turbohaler in such a way as to permit air to flow through the dosing channels and entrainment ports and out through the mouthpiece. A large three way tap permitted compressed air to be directed through the "spaceship" and hence the Turbohaler as required (fig 1). A flow of 60 l/min, calibrated using a rotameter (Fischer and Porter Ltd, UK), was used for all experiments.

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Figure 1 Particle sizing using laser particle sizer. The Turbohaler is supported in a “spaceship” permitting air to flow freely into the “spaceship”, through the dosing channels and entrainment ports of the Turbohaler, and out via the spiral mouthpiece. The pattern of airflow is unaltered by the “spaceship”. Compressed air flowing at 60 l/min can be directed through the Turbohaler, when required, using a large three way tap.

Figure 2 Particle size distribution of aerosol generated by an amiloride-containing Turbohaler (histogram) compared with that from a budesonide-containing Turbohaler (continuous line) as assessed with a Malvern MasterSizer laser particle sizer.

The spaceship also permits rotation of the Turbohaler turning grip and hence the dosing channels within the Turbohaler may be loaded without removing the Turbohaler from the spaceship.

ASSESSMENT OF DOSE DELIVERED

For each experiment the dosing channels were loaded and the powder within the dosing channels was then blown out of the Turbohaler onto a filter (Kendall Curity Anaesthesia Filter). Ten doses were delivered for each experiment. Seven experiments were performed using the amiloride-filled Turbohalers and 10 experiments with the commercial budesonide Turbohalers.

The amount of amiloride deposited on the filters and mouthpieces was measured using the following method. The filters and mouthpieces were washed with 100 ml 0.13% saline; 4.9 ml of 0.1M HCl was added to 40 ml of the filter wash and the solution was made up to 50 ml with 0.13% saline. The absorbance ($\lambda =$

Mean (SD) drug delivery from an amiloride-filled Turbohaler (n = 7) and a commercial budesonide Turbohaler (n = 10) at a flow rate of 60 l/min

	Amiloride (µg/dose)	Budesonide (µg/dose)
Mouthpiece	17.8 (6.5)	61.5 (14.0)
Filter	246.3 (40.4)	142.6 (16.4)
Total	264.0 (41.2)	204.0 (19.6)

362 nm) of each sample was measured in duplicate on a spectrophotometer (Hitachi U-2000). The concentration of amiloride in the filter and mouthpiece washes was calculated using the extinction coefficient of amiloride in 0.13% saline (ϵ 1% 1 cm = 610). The amount of amiloride (µg/dose) could then be calculated for each of the washes. A maximum error of 3.4% was obtained when a known concentration of amiloride was assayed using this method.

The quantity of budesonide was measured as follows. The filters and mouthpieces were washed with approximately 40 ml ethanol and the volume of each wash was then made up to a total of 50 ml with ethanol. The absorbance ($\lambda = 243$ nm) of each sample was measured in duplicate on a spectrophotometer (Hitachi U-2000). The concentration of budesonide in each of the washes was calculated using the absorbance of a solution containing a known concentration of budesonide. The standard curve for budesonide was linear ($r^2 = 1.00$) for concentrations between 1 and 30 µg/ml.

ASSESSMENT OF PARTICLE SIZE

The sizes of particles from the amiloride-filled Turbohalers were measured using a Malvern MasterSizer X laser particle size analyser (Malvern Instruments Ltd, UK). Turbohalers were placed in a “spaceship” and the micronised amiloride powder blown across the path of the laser. For comparison, the particle size distribution from the 200 µg commercial budesonide Turbohaler was measured using the same method. This approach to particle sizing aerosols generated by dry powder inhalers has been used in previous studies.^{10 11}

Results

The mean total output from both the amiloride-filled Turbohaler and the commercial (200 µg) budesonide Turbohaler is shown in the table. The proportion of amiloride deposited on the mouthpiece was much lower than that of budesonide, but the total dose delivered was higher for amiloride. The variability in the dose of amiloride delivered was greater than that of budesonide.

The mean (SD) volume median diameter of the dose delivered from the amiloride-filled Turbohaler was 3.80 (0.68) µm compared with 3.07 (1.47) µm from the commercial budesonide Turbohaler. The particle size distribution of the aerosols generated by the amiloride and budesonide-containing Turbohalers is illustrated in fig 2.

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Discussion

These results suggest that doses of amiloride, similar to those delivered via jet nebulisers, could be delivered efficiently to the lungs of patients with cystic fibrosis using a Turbohaler.

The results obtained using the Malvern MasterSizer show that the particle size distribution obtained using amiloride was similar to that generated by commercial Turbohalers containing budesonide. The slightly broader spread of particle sizes and slightly larger mass median diameter are likely to be related to the microniser used. Although this method for particle sizing aerosols generated by Turbohalers has been used before,^{10,11} the figures for volume median diameter cannot be used to calculate the mass median aerosol diameter since the particles are not spheres. Hence the results presented here illustrate qualitative changes in the aerosol characteristics and not quantitative changes in the mass median aerosol diameter.

The dose delivered from the amiloride Turbohaler was more than 200 µg while the variability in the dose delivered was also greater. This is probably because we used micronised, non-spheronised, powder which will be denser, leading to an increased dose, but will tend to flow less smoothly leading to greater inconsistencies in the filling of the dosing channels within the Turbohaler. Reproducibility might be increased if the powder could be spheronised.

A recent radiolabelled deposition study using jet and ultrasonic nebulisers¹² found that the mean dose of amiloride delivered to the lungs of patients with cystic fibrosis from a 1 mg initial dose was 103 µg using an ultrasonic nebuliser and 53 µg with a jet nebuliser. As in previous studies with nebulisers a wide range was observed in the dose delivered to the lungs. A recent radiolabelled deposition study suggested that approximately 27% of the budesonide contained in a 200 µg Turbohaler might be delivered to the lungs of healthy individuals when inhaling at approximately 60 l/min through the device,¹³ giving a lung dose of 54 µg. Our data suggest that similar results could be obtained when using Turbohalers containing amiloride. If higher lung doses were deemed desirable, it would be a simple matter to take a second dose from the Turbohaler or, alternatively, devices dispensing 400 or 500 µg could be used.

As with any dry powder inhaler, the efficiency of such a delivery system would obviously be limited in very young patients and those with extensive disease since the efficiency of delivery to the lower respiratory tract is determined to a large extent by the inspiratory effort generated by the patient. Another potential problem associated with dry powder inhalers is that current devices deliver more than 50% of the dose to the upper airway, much of which is subsequently swallowed. This may be a problem with drugs such as amiloride which are absorbed from the gastrointestinal tract. However, strategies to

reduce substantially the gastrointestinal dose, such as mouth rinsing, are available.

Patients report that the daily requirement for time consuming treatments, especially when aerosols are utilised, is one of the most demanding aspects of living with cystic fibrosis.¹ This study, and a previous study in which gentamicin was administered via the Rota-haler,⁸ indicates that a wide range of drugs could be delivered to the lungs of patients with cystic fibrosis using dry powder inhalers which would substantially reduce the time taken to administer treatments. It is likely that novel aerosol delivery systems, which are both convenient and more efficient than existing devices, will become available in the near future, and some of these may be eminently suitable for the delivery of drugs used in the treatment of cystic fibrosis. Unfortunately the cost involved in obtaining approval from regulatory bodies for new formulations is considerable and the size of the potential market makes such developments unattractive for pharmaceutical companies. Development of convenient aerosol delivery systems containing drugs such as amiloride and antibiotics will probably only occur if physicians and patient interest groups can persuade pharmaceutical companies that such developments would be of great benefit to patients with cystic fibrosis, and work with them to facilitate approval of such delivery systems.

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