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Research Paper

Suitability of the Upper Airway Models Obtained from MRI Studies in Simulating Drug Lung Deposition from Inhalers

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Purpose. In this study, the suitability of the upper airway models, obtained by applying a magnetic resonance imaging method, in simulating *in vivo* aerosol deposition data is determined.
Methods. Depositions of salbutamol sulfate from two nebulizers in two models, one with constriction at the oropharynx (the constricted cast) and another model without that constriction (the wide cast), were determined.
Results. For the Sidestream and Ventstream nebulizer, 76 ± 3% (mean ± standard deviation) and 81 ± 2% of the emitted dose deposited in the constricted cast, whereas 51 ± 2% and 49 ± 3% of the emitted dose deposited in the wide cast, respectively. These values were in good agreement with *in vivo* data. Mostly, increasing nebulizer charge volume (by normal saline) from 2.5 ml to 5 ml increased significantly the lung dose. However, the lung doses from the Sidestream and Ventstream nebulizer with 2.5 ml charge volume via the wide cast were (1.37 ± 0.06 and 1.38 ± 0.05 mg) significantly larger than those for the constricted cast with 5 ml charge volume (0.87 ± 0.15 and 0.86 ± 0.21 mg, respectively) ($p = 0.005$).
Conclusions. The upper airway models closely simulated the *in vivo* deposition data. Optimizing the upper airway posture during inhalation via the nebulizers would be more efficient in increasing drug lung delivery than diluting their contents.

KEY WORDS: aerosols; nebulizers; upper airway models; upper airway posture.

INTRODUCTION

It has been shown that part of respirable particles (aerodynamic size of 1 to 5 μm) can be filtered by the upper airway (mouth and throat) (1–3). This role of the upper airway has made the formulation scientists to use models of the upper airway to predict more accurately the performance of an inhaler in the clinic (4–7). However, the methods that have been used to determine the upper airway shape for this purpose either were based on cadaveric studies (8) or observing the upper airway of subjects who were not inhaling via an inhaler (7). Thus, the upper airway models obtained by applying these methods cannot present the actual upper airway shape during inhalation via the aerosol devices and cannot simulate *in vivo* data as they are expected (6).

Recently, a magnetic resonance imaging (MRI) method has been developed that allows studying and three-dimensional reconstruction of the upper airways of subjects while inhaling via aerosol devices (9). However, this method requires several inhalations via an inhaler to scan the upper airway completely and also the subject needs to be in a supine position, which normally would not be taken during inhalation via an inhaler. Then, the suitability of the upper airway models obtained by applying this method in predicting *in vivo* results may be debatable. Hence, in this study, aerosol depositions in two upper airway models with different postures are compared with previously published *in vivo* data. Previous *in vivo* studies investigated deposition of monodisperse particles with aerodynamic size of 3.6 μm in subjects with different upper airway postures while inhaling via a straight tube (1,2). Then in this study to produce similar aerosol particles, salbutamol sulfate solution was nebulized via the Venstream and Sidestream jet nebulizers (10). As increasing the nebulizer charge volume by dilution decreases nebulizer dead volume (11), then these upper airway models were used to investigate the efficiency of this approach in improving drug delivery to the lungs.

MATERIALS AND METHODS

Materials

Brij 35 (polyoxyethylene lauryl ether) was purchased from Sigma-Aldrich (Chemie GmbH, Steinheim, Germany), glycerol was obtained from BDH Laboratory Supplies (Poole, England), salbutamol sulfate micronized powder was a gift from Glaxo Wellcome (Ware, UK), and salbutamol sulfate nebulizer solution for inhalation (5 mg in 2.5 ml, Ventolin Nebules, Allen & Hanburys, Middlesex, UK) was used.

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Methods

Manufacturing Upper Airway Models

Three-dimensional reconstructions of the upper airways of two healthy adult subjects with different postures (interindividual variations during inhalation via the aerosol devices) while inhaling via the Nebuchamber device (AstraZeneca, Kings Langley, UK) (performed in previous study) (9) were converted into stereolithographic format using computer programs written by MATLAB 6.0 (MathWorks, Inc, Natick, MA, USA). Then these files were used by a Dimension Machine 3D Printer (Stratasys, Eden Prairie, MN, USA) to produce upper airway models from ABS (acrylnitrile butadiene styrene) plastic. The models were prepared in four parts (oral cavity, oropharynx, larynx, and upper trachea), which were fastened to each other by nuts and bolts to form the complete upper airway model. Parafilm M flexible film at the split planes was used to airtight the models.

The upper airway postures were marked constriction by the tongue at the end of the soft palate in the oropharynx region, and wide open space at that position (Fig. 1A). In this paper, the cast of the upper airway with that constriction is denoted by the constricted cast, and the other by the wide cast. The cross-sectional area profiles of these upper airways, calculated according to the previously reported method (9), in different regions are illustrated in Fig. 1B.

Experimental Setup

The Sidestream (Medic-Aid, Bognor Regis, UK) and Ventstream (Medic-Aid, Bognor Regis, UK) jet nebulizers were operated by a Portaneb compressor (Profile Therapeutics, Bognor Regis, UK). It has been reported that nebulizing salbutamol sulfate (5 mg in 2.5 ml) by the Sidestream nebulizer produces aerosol particles with mass median diameter of 3.9 ± 1.9 (geometric standard deviation) μm, and 3.8 ± 2.1 μm by the Ventstream nebulizer (10).

Each nebulizer in the upright position was connected to the oral cavity of the upper airway cast. Then the cast was connected to a cup (to collect nebulizer drops formed from the deposition of the aerosol particles in the cast), and the cup to an extracting tube which contained glass wool plug (Fig. 2). The extracting tube was connected to a vacuum pump (Alcatel, Franklin Electric, Bluffton, IN, USA) to draw air at the rate of 30 L/min through the cast. The above experimental setup prevented contamination of the glass wool plug with the nebulizer drops formed from deposition of the aerosol particles in the cast.

In order to simulate the wet mucosa that naturally occurs in the upper airway, prior to each experiment run the cast was filled with a solution of 0.7 g Brij 35 in 100 ml of glycerol. Then the solution was emptied from the cast, and the cast was left up right for 15 min to drip-dry (4). The nebulizers were charged either with 2.5 ml (nominal volume) of the nebulizer solution, or the nebulizer solution diluted with 2.5 ml of normal saline. The nebulizers were operated for 15 min when charged with 2.5 ml solution or 20 min for otherwise to ensure that they past the sputtering point. As soon as the nebulizers started to operate, the vacuum pump was switched on to draw the aerosol particles through the casts.

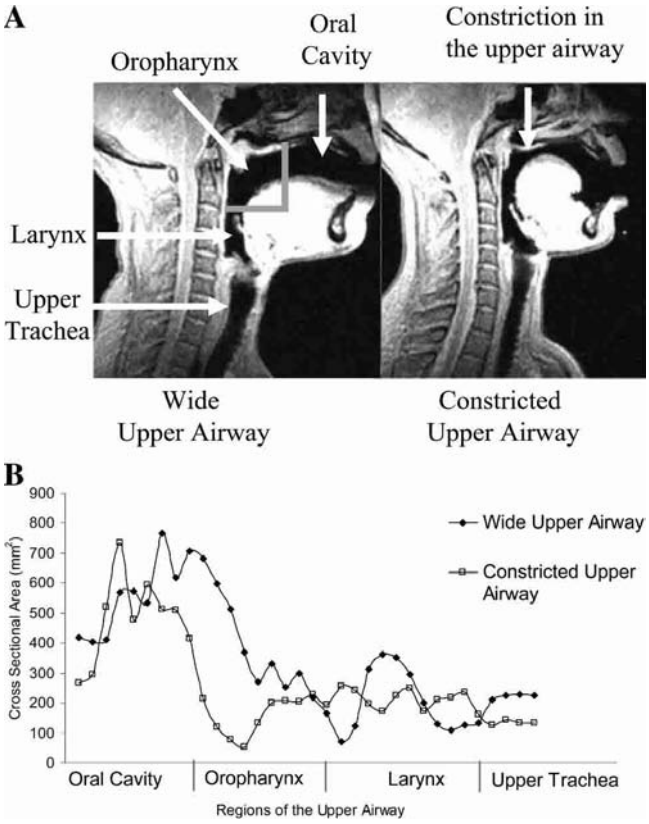

Fig. 1. (A) Midsagittal magnetic resonance images of the upper airways of two healthy adult subjects with different postures during inhalation via aerosol devices. The difference in the postures is the variation in the tongue position at the end of the soft palate in the oropharynx region (shown by arrow). (B) Cross-sectional area profiles of the upper airways in different regions. Open squares represent the constricted upper airway, which has constriction in the oropharynx region, and closed diamonds show the wide upper airway, which has wide space in that region. The gap between cross sectional areas in the oral cavity, larynx, and upper trachea is 5 mm in the imaging direction. In the oropharynx measurements, the right angle toward the oropharynx is divided into sections with 10° gaps, and the sections are extended to intersect with the oropharynx. The measured cross-sectional areas are perpendicular to the centreline (9).

Determination of Deposited Aerosol

At the end of each experiment run, the nebulizer, all parts of the cast, the cup, and the glass wool plug (filter) were washed separately with distilled water. The amount of salbutamol sulfhate in each wash was determined by spectrophotometeric analysis at 276 nm from a standard curve (11,12). Pilot testing using only normal saline in the nebulizers showed that other ingredients in each experiment run did not have absorbance at 276 nm. Also rinsing the cast and filter with known concentrations of salbutamol sulfate revealed that these parts did not adsorb the drug, and other ingredients in the experiment run did not change the peak absorbance of the drug. At least 92% of the nominal charged dose in the nebulizer was recovered after each experiment run. Each deposition study was replicated six times.

Statistical Analysis

In order to compare the deposition values of salbutamol sulfate in the filter, initially a one-way ANOVA was carried

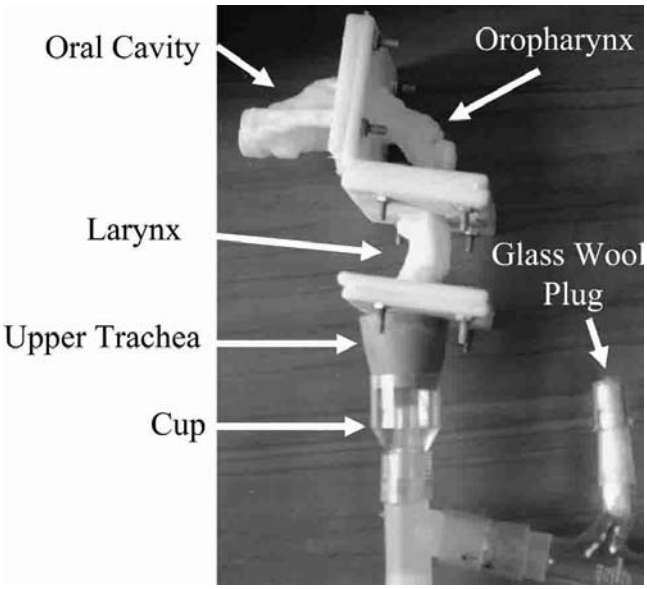

Fig. 2. Experimental setup used to evaluate deposition of aerosol particles from the nebulizers in the upper airway casts. In this figure, different parts of one of the casts are also illustrated.

out, but it was found that the assumption for equality of the variances was not valid (p value for test of homogenenity of variances was less than 0.05). Then a Kruskal-Wallis test followed by two-tailed Mann-Whitney *U* tests with Bonferroni correction to the alpha level (p, 0.05/3 comparisons for each device = 0.0167) were conducted (13,14).

Two-tailed Mann-Whitney *U* tests were also conducted to compare drug depositions in similar parts of the casts for the same nebulizer. Then, probability values of $p < 0.05$ were considered significant. The values given in Results section are mean ± standard deviation.

RESULTS

Simulation of *in Vivo* Deposition Data

Figure 3 presents percents of the emitted dose that deposited in the casts and filters, while the nebulizers were charged with 2.5 ml of the nebulizer solution. For the constricted cast by nebulizing via the Sidestream and Ventstream nebulizers 76 ± 3% and 81 ± 2% of the emitted dose were deposited in the cast, and 24 ± 3% and 19 ± 2% were deposited in the filter, respectively. Whereas for the wide cast, 51 ± 2% and 49 ± 3% of the emitted dose were deposited in the cast, and 49 ± 2% and 51 ± 3% were deposited in the filter when the Sidestream and Ventstream nebulizers were used, respectively. In this figure, the reported values (1,2) for deposition of monodisperse particles (3.6 μm aerodynamic diameter) in the throat and lungs of a subject forming a wide space in the throat (class A) and another subject forming a constricted space in the throat (class C) during inhalation of the aerosol particles are also presented. It can be seen that aerosol depositions in the throat (76%) and lungs (24%) of the subject with constricted throat are in good agreement with the deposition data obtained from the constricted cast. The deposition data in the throat (42%) and lungs (58%) of the subject with wide space in the throat are also in good agreement with the results of the wide cast.

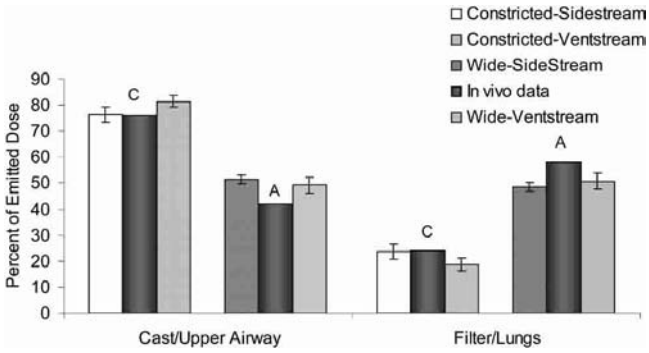

Fig. 3. Deposition of the fraction of the emitted dose from the nebulizers in the cast and filter. In this figure, *in vivo* deposition data, reported in the previous studies (1,2) for postures similar to those that were considered in this study, are also included. The deposition data for a subject with wide open space in the throat during inhalation of the aerosol particles is denoted by "A," and the deposition data for a subject with constriction in the throat during inhalation of the aerosol particles is denoted by "C." Horizontally hatched bars represent the wide cast with the Ventstream nebulizer, chequered bars indicate the wide cast with the Sidesream nebulizer, white bars denote the constricted cast with the Sidestream nebulizer, vertically hatched bars show the constricted cast with the Ventstream nebulizer, and gray bars denote the *in vivo* data. Error bars indicate standard deviation, (n = 6).

Drug Deposition Distribution in the Casts

Drug deposition in different parts of the casts, and the cup while the nebulizers charged with 2.5 ml of the nebulizer solution are illustrated in Fig. 4 (the amounts of the drug that were left in the nebulizers and deposited in the filter are not shown). The amounts of salbutamol sulfate deposited in the cup by using the constricted cast (1.16 ± 0.08 mg for the Sidestream nebulizer and 1.48 ± 0.19 mg for the Ventsream nebulizer) were significantly larger than those for the wide cast (0.54 ± 0.12 mg for the Sidestream nebulizer $p = 0.005$, and 0.48 ± 0.21 mg for the Ventsream nebulizer, $p = 0.005$). Similarly, the amounts of salbutamol sulfate deposited in the oropharynx part by using the constricted cast (0.26 ± 0.1 mg for the Sidestream nebulizer and 0.34 ± 0.13 mg for the Ventsream nebulizer) were significantly larger than those for

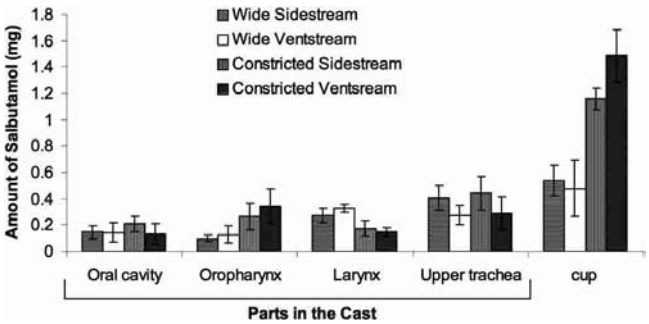

Fig. 4. Drug deposition distribution in the casts, while nebulizers were charged with 2.5 ml nebulizer solution. This demonstrates that the aerosol deposition distribution in the upper airway casts is not uniform. Horizontally hatched bars represent the wide cast with the Sidestream nebulizer, white bars denote the wide cast with the Ventstream nebulizer, vertically hatched bars show the constricted cast with the Sidestream nebulizer, and chequered bars indicate the constricted cast with the Venrsream nebulizer. Error bars indicate standard deviation, (n = 6).

the wide cast (0.09 ± 0.06 mg for the Sidestream nebulizer p = 0.005, and 0.13 ± 0.06 mg, p = 0.02, for the Ventsream nebulizer). Whereas the amounts of salbutamol sulfate deposited in the larynx part by using the wide cast (0.27 ± 0.06 mg for the Sidestream nebulizer and 0.33 ± 0.03 mg for the Ventsream nebulizer) were significantly larger than those for the constricted cast (0.17 ± 0.06 mg for the Sidestream nebulizer p = 0.03, and 0.15 ± 0.03 mg, p = 0.005, for the Ventsream nebulizer). Significant differences for drug depositions in the oral cavity and upper trachea parts by using both nebulizers were not observed.

Effect of the Nebulizer Charge Volume

Figures 5A and 5B illustrate the effect of the charge volume in the Ventstream and Sidestream nebulizers, respectively, on drug deposition in the casts (including the cup) and filters (the amounts of the drug that were left in the nebulizers are not shown). Figure 5A shows that by increasing nebulizer charge volume the amount of salbutamol sulfate deposited in the filter increases from 0.54 ± 0.07 mg to 0.86 ± 0.21 mg by using the constricted cast, and for the wide cast that increases from 1.38 ± 0.05 mg to 1.81 ± 0.14 mg. Similarly, Fig. 5B illustrates that the amount of the drug deposited in the filter increases from 0.70 ± 0.12 mg to 0.87 ± 0.15 mg by using the constricted cast, and for the wide cast it increases from 1.37 ± 0.06 mg to 1.73 ± 0.09 mg. For both casts and nebulizers (apart from the constricted cast used by the Sidestream nebulizer) the amounts of drug deposited in the filter with 5 ml of nebulizer charge volume were significantly larger than those with 2.5 ml nebulizer charge volume ($p < 0.0167$). Furthermore, the wide cast for both nebulizers with lower nebulizer charge volume allowed significantly more amounts of drug to reach the filter than the constricted cast with higher nebulizer charge volume ($p < 0.0167$).

Figure 5 also indicates that by increasing the nebulizer charge volume the amounts of salbutamol sulfate deposited in the casts did not change considerably (apart from the Ventsream nebulizer used with the wide cast).

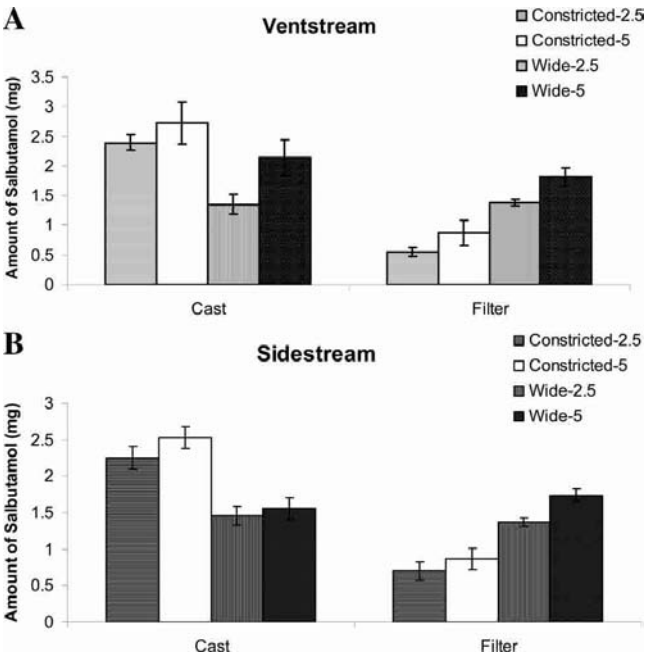

Fig. 5. The effect of nebulizer charge volume on the amount of salbutamol sulfate deposited in the cast (including the cup) and filter by using (A) the Ventstream, and (B) the Sidestream nebulizer. This demonstrates increasing drug deposition in the filter by increasing nebulizer charge volume (diluting with normal saline). Horizontally hatched bars represent the constricted cast with 2.5 ml nebulizer charge volume, white bars denote the constricted cast with 5 ml nebulizer charge volume, vertically hatched bars show the wide cast with 2.5 ml nebulizer charge volume, and chequered bars indicate the wide cast with 5 ml nebulizer charge volume. Error bars indicate standard deviation, (n = 6).

DISCUSSION

We have shown that the deposition data determined from *in vitro* experiments by employing the upper airway casts, which were obtained from MRI studies (9), mimic closely *in vivo* deposition data. These *in vivo* studies have shown that 71–75% of the inhaled aerosol (aerodynamic size of 3.6 μm) deposits in the upper airways with constricted posture during inhalation (1) and this is in good agreement with our findings, which were in the range 76–81% for the constricted cast. The same *in vivo* studies showed that fraction of the inhaled dose that deposits in the upper airway of subjects with a wide open space in their throats during inhalation ranges from 10% to 48% (1,2). Again this is in good agreement with deposition data that were determined by the wide cast, which were in the range 49–51%. It can be seen that the drug deposition in the wide cast matches part of the aerosol deposition range observed in the clinical studies. The lack of achieving deposition of 10% of the emitted dose in the wide cast, may be explained that there are other postures with wide space in the throat during inhalation that were not considered in this study. Further studies are required to determine these postures.

We used split casts of the upper airway to determine those parts that are more effective in aerosol deposition in the cast. Higher drug deposition in the oropharynx part of the constricted cast compared to the wide cast can be explained due to the marked constriction in this region for the constricted cast. Also, higher aerosol deposition in the larynx part of the wide cast compared to the constricted cast might be explained by the slight constriction in this region for the wide cast (cf. Fig. 1B). However, it should be noted that relocation of the aerosol deposits in the casts (collection of aerosol deposits in the cup), due to high aerosol deposition, may alter the original aerosol deposition distribution. Then, in order to determine more accurately the particle flow and deposition in the upper airway casts while using nebulizers, other techniques such as particle imaging velocimetry need to be used (15). These observations show that aerosol deposition in the upper airway casts is not uniform, and constrictions in the upper airway due to certain upper airway postures or the anatomy of the upper airway may increase aerosol deposition in the throat.

Increasing nebulizer charge volume by diluting with normal saline increased drug delivery to the filter, whereas the amounts of salbutamol sulfate deposited in the upper airway casts remained rather unchanged. This observation may be explained that by increasing the volume of nebulizer solution, the amount of aerosol droplets that deposits in the cast also increases. However, because the droplets now contain a lower drug concentration, then increasing the aerosol deposition in the cast does not result in more drug deposition.

Although increasing nebulizer charge volume increased the amount of the drug delivered to the filter, drug delivery though the constricted cast was always significantly less than that for the wide cast. This observation suggests that modifying the patient upper airway posture during inhalation to increase drug lung deposition via nebulizers would be more effective than increasing nebulizer charge volume by dilution. Increasing nebulizer charge volume also increases the nebulisation time and this may compromise patient compliance (16).

In this study, we used a constant flow through the casts. As during the MRI studies the subjects were almost inhaled at constant airflow, and the upper airway images only during inhalation were acquired, then applying constant flow through the casts was more appropriate than a sinusoidal flow (10,11). However, the results of this study will overestimate the deposition data that were based on the total amount of the drug that was delivered to the patient (17). This is because part of the inhaled drug was wasted during patient exhalation (17,18). Depending on the chosen nebulizer system and drug, 32.36 ± 3.61% (17) and 12.2 ± 3.4% (18) of the nominal dose have been reported to be collected on the exhalation filters.

In conclusion, the upper airway casts that are obtained from the MRI studies closely simulate clinical data regarding aerosol deposition in the upper airway and lungs. This study also suggests that improving the upper airway posture during inhalation would deliver more amounts of drug to the lungs than increasing nebulizer charge volume by dilution.

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