Improvement of nebulised antibiotic delivery in cystic fibrosis

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Abstract

Aim—To investigate deposition patterns and to assess the delivery rate of two nebuliser systems in children with cystic fibrosis (CF).

Methods—Thirty three children with CF on regular treatment with nebulised antibiotics had radioisotope scans performed using technetium-99m labelled aerosol antibiotic generated by a Ventstream nebuliser (median mass diameter (MMD), 3.3 µm; delivery rate, 0.075 ml/min) under conditions similar to their routine home practice. The inhomogeneity of the images was scored on a 1–10 rating scale (a low score indicating even distribution of the antibiotic), and stomach deposition was measured as a percentage of overall deposition. Twenty patients had a repeat scan using an Optimist nebuliser (MMD, 1.8 µm; delivery rate, 0.02 ml/min).

Results—The mean inhomogeneity scores were 5.4 in the Ventstream group and 3.5 in the Optimist group. Mean stomach deposition was 17.3% in the 33 patients using the Ventstream nebuliser. There was an inverse relation between height and stomach deposition ($r = 0.69$). In the 20 patients who had both nebulisers, the mean percentages of stomach deposition for the Ventstream and Optimist nebulisers were 11.8% and 1.6%, respectively. The Ventstream nebuliser delivered antibiotic at an average 2.8 times faster rate than the Optimist nebuliser.

Implications—A smaller particle size results in a more homogenous distribution of the antibiotic in the lungs with decreased stomach deposition. This should not be seen as a recommendation to use the Optimist nebuliser because more antibiotic was delivered to most parts of the lung with the Ventstream because of its increased delivery rate.

(Arch Dis Child 1999;80:348–352)

Keywords: cystic fibrosis; nebulised antibiotics; nuclear medicine; particle size

Nebulised antibiotics are an important component of the treatment of individuals with cystic fibrosis (CF).^{1–4} In recent years, the use of nebulised antibiotics has increased following reports that early treatment can prevent or delay the onset of chronic pseudomonas infection.^{5–7} Other studies have documented reduced bacterial counts and improved respiratory function in patients treated with nebulised tobramycin

compared with controls.⁸ These studies have increased the number of patients with CF who receive nebulised antibiotic treatment: 50% of patients attending the regional paediatric CF Unit (RPCFU) at St James's University Hospital in Leeds are currently treated with nebulised colistin or tobramycin.

The use of nebulised antibiotics is time consuming and expensive. It is therefore important that the antibiotic should be deposited in the lungs to ensure efficient treatment. Swallowed antibiotic reduces the efficacy and efficiency of the treatment. Low antibiotic uptake within the lungs or poor antibiotic distribution in the lungs may also explain a lack of treatment response in some patients. There have been a number of studies that have assessed drug delivery rates and deposition patterns in the lung.^{9–13} However, the process is governed by complex relations between many factors such as particle size, breathing pattern, and method of inhalation,^{14 15} as well as functional and anatomical status of the lung. Relatively few studies have been conducted on children,^{16 17} although it has been noted that deposition patterns and rates may differ significantly from those reported for adults.¹⁸

Our study investigated the deposition of antibiotic aerosols delivered by the nebuliser system (Ventstream; Medic-Aid Ltd, Bognor Regis, West Sussex, UK) currently used in the RPCFU at St James's to determine the efficiency of the patient's usual practice of delivery and whether distribution patterns could be improved by altering droplet size distribution.

Methods

PATIENTS

Our studies were performed on 33 children (20 girls, 13 boys) with CF (all had their diagnosis based on genotyping, two positive sweat tests, and clinical features compatible with the disease). The median age was 12 years (range, 4.7–17.7). Twenty of these patients went on to have the test repeated using the second nebuliser. All patients were receiving regular nebulised antibiotics as part of their treatment. The median forced expiratory volume in one second (FEV₁) was 62% of that predicted (range, 33–109%), median forced vital capacity (FVC) was 82% of that predicted (range, 40–144%), median Chrispin Norman α ray score (CNS) was 14 (range, 3–30), and median Shwachman score was 80 (range, 55–100). Ethics committee approval and written informed consent were obtained for the study.

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Accepted 5 October 1998

Figure 1 Variation of percentage stomach deposition with height.

Figure 2 Percentage of deposition that ended up in the stomach for each of the 20 patients who had both Ventstream and Optimist scans.

PROCEDURES

Nebulised antibiotic treatment was delivered in a manner that closely resembled the clinical situation; the antibiotic used already formed part of the patient's current treatment (19 patients used colistin and 14 patients used tobramycin). The antibiotics were added to a diethylenetriaminepenta-acetic acid (DTPA) solution labelled with technetium-99m. The activity of the technetium-99m administered was 80 MBq scaled for age, leading to an effective dose equivalent to the patient of 0.6 mSv. Aerosols generated from this mixture contain antibiotic and radiolabel and it was assumed that the distribution of radiolabel in the respiratory tract reflected that of the drug. Previous studies demonstrate that there is no dissociation of the antibiotic and tracer and that the radioisotope has little effect on the particle size.¹⁹⁻²¹

Figure 3 Images demonstrating considerable stomach deposition with the Ventstream nebuliser.

Figure 4 Inhomogeneity scores of the Ventstream and Optimist images from the 20 patients who used both antibiotic delivery systems. The higher the inhomogeneity score, the more uneven the distribution of antibiotic in the lungs.

The patients used a Ventstream nebuliser connected to a compressed air supply running at the manufacturer's recommended rate of 6 l/min, generating particles with a mass median diameter (MMD) of 3.3 μ m, as measured by the manufacturer using a Malvern mastersizer (Malvern Instruments, Malvern, Worcs, UK). The antibiotic was inhaled via a mouthpiece and a noseclip was used in all cases. A noseclip is not used in clinical practice but was necessary to minimise radioactive environmental contamination. No additional instruction on breathing technique was given. The nebuliser body was contained in a lead shield and filters trapped exhaled particles to minimise environmental contamination. The patients used the nebuliser for 10 minutes in each case rather than nebulising to a fixed end point. Directly after nebulisation, the patients were imaged using a gamma camera (Siemens Basicam or Siemens Orbiter; Siemens, Hoffman Estates, Illinois, Chicago, USA) with a low energy, all purpose collimator. Posterior views were acquired for 200 k counts. Data were stored and processed on a Sun SPARC workstation running MAPS 10000 software (Link Medical, Marlow, Bucks, UK). SPECT imaging, although giving better visualisation of distribution patterns, was not possible because patients were too young to keep still for the required amount of time. Lung function tests (FEV₁, FVC) were performed using a Vitalograph compact spirometer (Vitalograph Ltd, Maids Morton, Bucks, UK).

Twenty of the 33 patients (10 girls, 10 boys) attended the isotope department a second time, at least a week after the first visit. A similar protocol was followed but on this occasion the patients used an Optimist (Medic-Aid Ltd) nebuliser connected to a compressed air supply running at the recommended rate of 10 l/min (MMD, 1.8 μ m).

Regions of interest were drawn over the lungs and the stomach on the acquired posterior views. An assessment of percentage of antibiotic swallowed was made by calculating the ratio of counts in the stomach region to those in the lung and stomach regions combined.

An experienced nuclear medicine observer ranked and scored the homogeneity of the lungs. The observer was blinded to all other

Figure 5 Images from the same patient using the Ventstream and the Optimist nebuliser. The antibiotic is distributed much less evenly throughout the lungs when the Ventstream nebuliser is used.

data and the images were randomised. Scores ranged from 1 to 10 with a score of 10 representing maximal inhomogeneity in our patient group. Images containing one high intensity hot spot were judged to be less homogenous than images containing many low intensity hot spots.

To compare the antibiotic delivery rates of the Ventstream and Optimist nebulisers, the rates at which counts were acquired for the images from each nebuliser (normalised for activity administered to the reservoir) were calculated for the patients who used both nebulisers.

Results

STOMACH DEPOSITION

The mean percentage of administered antibiotic deposited in the stomach for the Ventstream nebuliser was 17.3% (range, 1.7–49%). There was a clear inverse relation between height and stomach deposition ($r = 0.69$) as shown in fig 1.

The Ventstream and Optimist stomach deposition for the 20 patients who used both nebulisers is shown in fig 2. In this patient group, the mean percentages of stomach deposition were 11.8% for the Ventstream and 1.6% for the Optimist (range, 0.3–22.0% for the Ventstream; 0.5–7.0% for the Optimist). The mean values were significantly different ($p < 0.01$ (paired t test)). A typical difference in stomach deposition for the same patient using the Ventstream nebuliser and then the

Optimist nebuliser on a separate occasion is shown in fig 3.

ANTIBIOTIC DISTRIBUTION WITHIN THE LUNGS

The mean inhomogeneity observer score of the 33 patients was 5.4 for the Ventstream nebuliser. In the 20 patients who used both nebulisers, the mean inhomogeneity observer scores for the Ventstream and Optimist were 5.4 and 3.5, respectively ($p < 0.001$ (paired t test)). This shows that a more homogenous distribution is obtained with a smaller particle size. Figure 4 shows the Ventstream and Optimist inhomogeneity scores for the patients who used both nebulisers.

Figure 5 shows the Ventstream and Optimist images for a typical patient. The Ventstream image shows antibiotic forming clumps within the lungs, whereas the Optimist nebuliser produces a much more uniform deposition pattern.

There was a highly significant correlation between FEV_1 ($r = -0.43$; $p < 0.02$), CNS ($r = 0.52$; $p < 0.01$), and the Ventstream inhomogeneity score. Figure 6 shows that as the clinical condition worsens there is a tendency for the antibiotic to be deposited more unevenly. Two exceptions to this trend are ringed on fig 6 and relate to the same patients. These both have a good clinical condition but very poor antibiotic distribution for reasons suggested in the discussion. When these two patients are excluded from the analysis the correlation coefficient becomes stronger (FEV_1 : $r = -0.62$, $p < 0.001$; CNS: $r = 0.65$, $p < 0.005$). The images from one of these outliers are shown in fig 7.

There is also a strong and highly significant correlation between FEV_1 ($r = -0.61$; $p < 0.02$), CNS ($r = 0.72$; $p < 0.001$), and the Optimist inhomogeneity score as shown in fig 8.

ANTIBIOTIC DELIVERY RATE

The Ventstream nebuliser delivered antibiotic at an average rate 2.8 times faster than the Optimist nebuliser but there was high inter-patient variability (range, 0.9–5.2).

Discussion

Current clinical practice at St James's for nebulising antibiotic is to use a Ventstream nebuliser but these results demonstrate potential

Figure 6 Relation between observer inhomogeneity score and clinical condition for the Ventstream nebuliser. In the ringed cases, the inhomogeneity is more likely to be a result of airways geometry than clinical condition.

Figure 7 Images from a patient with good clinical condition but poor antibiotic distribution with the Ventstream nebuliser. The distribution is more likely to be a result of airways geometry than disease processes. Distribution is greatly improved with the Optimist nebuliser.

problems with regard to lung deposition patterns and the amount of stomach deposition (on average, 17% of antibiotic delivered to the body), particularly with smaller children.

The results show important differences in the distribution of antibiotic delivered by the Ventstream and Optimist nebulisers. These may be explained by the difference in MMD between the two nebulisers, which affects the amount of antibiotic that is swallowed and the distribution of antibiotic within the lungs. Stomach deposition of the antibiotic is likely to be a result of inertial impaction of the particles in the region of the oropharynx and this effect will be greater for particles with a larger MMD because of their increased inertia. The correlation between swallowing and height can also be explained in this way because taller children will have wider airways and a larger radius of curvature. They may also be more skilled in using the nebuliser.

It is possible that patients' breathing techniques were improved when they used the Optimist nebuliser because of a training effect from the previous use of the Ventstream nebuliser with a noseclip. The order was not randomised because the original study protocol specified that patients were only to be assessed with the Optimist nebuliser if their Ventstream images were very heterogeneous or there was a considerable amount of stomach deposition. This order effect is likely to be small because patients only used the Ventstream with a noseclip once and the minimum time between studies was one week.

Problems were encountered in the analysis of the degree of swallowing of the antibiotic. Patients were not asked to drink after nebulisation and in most cases it was not possible to discriminate between deposition in the upper airways and upper digestive tract. Stomach deposition only has been calculated. Deposition within the oesophagus and mouth has not been included. Thus, extrapulmonary deposition might have been underestimated. No correction was made for differences in attenuation between the stomach and lungs because the study was largely concerned with inpatient comparisons.

Large amounts of stomach deposition lead to an inefficient use of both expensive antibiotic and patient's time. Switching to a smaller particle size reduces the amount swallowed, particularly in smaller patients, but probably at the expense of overall lung delivery. The fact that as much as 50% of delivered antibiotic is swallowed in small and young patients may be a cause for concern, particularly because patients are commonly started on nebulised antibiotics from the age of 1 year. Any attempt to relate dosimetry to outcome will be difficult for prophylactic antibiotics, particularly because the amount of antibiotic that is swallowed will not necessarily be known.

In general, a more homogenous distribution was obtained using the Optimist nebuliser and this is likely to be because of reduced deposition by inertial impaction. There is a correlation between clinical condition (as measured by CNS and FEV₁) and homogeneity. In general, the worse the patient's condition, the less homogenous the antibiotic distribution within the lungs. This would appear to indicate that narrowing of the bronchial tree or, possibly, increased sticky secretions lead to increased deposition by inertial impaction and, therefore, less homogenous images. However, there were two patients who had very inhomogeneous images but good clinical condition. The images from one of these patients are shown in fig 7. Some of the hot spots appear to be located at points where major airways bifurcate, suggesting that this deposition is a result of airways geometry, rather than poor clinical condition. The stronger correlation with the inhomogeneity of the Optimist images also supports this view because a smaller particle size is less likely to suffer inertial impaction at an airways bifurcation. Figure 7 should be

Figure 8 Relation between observer inhomogeneity score and clinical condition for the Optimist nebuliser system.

contrasted with the Ventstream image shown in fig 5, where the inhomogeneity is much more diffuse.

Large amounts of stomach deposition or poor distribution of antibiotic in the lungs may explain the poor clinical response of some patients to nebulised antibiotics. The results of our study suggest that nebulised antibiotic treatment may be least effective in patients with poor clinical condition. However, it is difficult to assess the efficacy of any antibiotic regimen without long term follow up studies and, therefore, it is also difficult to draw conclusions about the treatment implications of our findings. A common assumption is that a homogenous distribution is the more desirable, but this may not be valid if antibiotic is preferentially deposited at sites or possible future sites of infection. Antibiotic may be deposited in clumps where there are increased sticky secretions and these may be the most likely areas for infection to arise. A homogenous distribution may be desirable for future treatments (such as gene therapy) that are delivered in aerosol form.

The major disadvantage of the Optimist nebuliser that limits its clinical use is the low delivery rate. The total amount of antibiotic delivered to almost all regions of the lungs when patients nebulised for 10 minutes was greater for the Ventstream nebuliser, despite the fact that a large proportion of antibiotic was being deposited in the stomach. The design of the Optimist nebulisers eliminates larger particles from the aerosol mist to reduce the MMD, resulting in a lower antibiotic delivery rate. It would be possible to overcome the problem of low delivery rate by increasing nebulisation time, but this might compromise patient adherence to treatment protocols. The increased homogeneity of the antibiotic distribution delivered by the Optimist nebuliser may, however, make less frequent drug delivery adequate although, as discussed above, this assumes that a homogenous distribution is desirable. The ideal solution might be a faster delivery, smaller particle size nebuliser. A further potential disadvantage of the Optimist nebuliser is that the small particle size might enable it to reach very small airways and alveoli, leading to undesirable systemic absorption of the antibiotic.

CONCLUSIONS

Our study has shown that a nebuliser in current clinical use (Ventstream) results in a considerable amount of antibiotic being swallowed, especially in younger children, and that the proportion of nebulised antibiotic in the stomach might be reduced by reducing the MMD of the aerosol.

A nebuliser with a smaller particle size produced a more homogenous distribution in the lungs and reduced stomach deposition. The design of the Optimist nebuliser achieves this at the expense of antibiotic delivery rate. The Ventstream nebuliser delivered more antibiotic to the lungs after the same nebulisation time than the Optimist nebuliser. It may be possible to develop a nebuliser that delivers a fine aerosol to the lungs at an increased rate.

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