

Deposition of carbenicillin aerosols in cystic fibrosis: effects of nebuliser system and breathing pattern

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ABSTRACT Antibiotic aerosol treatment is successful in treating *Pseudomonas* infection in some patients with cystic fibrosis, but the amount of drug reaching the lungs is unknown. The deposition patterns of carbenicillin aerosols delivered from two commercially available nebuliser systems (the Turret nebuliser plus Maxi compressor and the Inspiron nebuliser plus Traveller compressor) have been compared in six patients with cystic fibrosis during tidal breathing. The aerosol mass median diameters were 3.2 and 7.3 μm . In addition, the aerosol from the Turret-Maxi nebuliser system was inhaled by a combination of tidal and deep breathing. After two minutes' breathing via a mouthpiece the mean (SEM) deposition in the lungs was 15.60 (1.5) mg carbenicillin with the Turret nebuliser plus Maxi compressor, but only 6.54 (1.09) mg with the Inspiron nebuliser plus Traveller compressor; the distribution pattern within the lung was significantly more peripheral with the former nebuliser system. These differences may be ascribed partly to the smaller droplet size from the Turret system and partly to the higher nebulisation rate from the more powerful Maxi compressor. Tidal plus deep breathing produced a further small but non-significant increase in lung aerosol deposition. A seventh patient, who failed to complete the trial, had little aerosol deposited in his lungs because he inhaled through his nose. These results emphasise the importance of correct selection of nebuliser equipment for antibiotic aerosol treatment.

Antibiotic aerosol treatment originated in the 1940s, when various antibiotics were inhaled either as nebulised solutions^{1,2} or as dry powders³ to treat respiratory tract infections. Although this practice waned in popularity, it has recently been revived, particularly to treat *Pseudomonas* infection in some patients with cystic fibrosis.⁴⁻⁷ The efficacy of aerosol antibiotic treatment may depend in part on the choice of nebuliser equipment; in vitro laboratory studies have suggested that the quantities of gentamicin,⁸ carbenicillin,⁹ ceftazidime, and colistin¹⁰ reaching the lungs may vary widely according to the type of nebuliser and compressor.

Relatively little is known about the site of deposition of antibiotic aerosol within the respiratory tract, and the extent to which the aerosol penetrates to the more peripheral lung regions. In this study in patients with cystic fibrosis we have used radiotracer techniques to assess the deposition patterns of antibiotic aerosols delivered from two commercially available

nebuliser systems with widely differing droplet size distributions. We have also compared the deposition following tidal breathing with the deposition following a combination of tidal and deep breaths.

Methods

Radioaerosol studies were performed on seven patients with cystic fibrosis (five men, two women, age range 22-48 years) selected from outpatient clinics at the Brompton Hospital, London. All were being treated with antibiotics by aerosol on a regular basis. Forced expiratory volume in one second (FEV₁) ranged from 16% to 57% of the predicted value.¹¹ Informed consent in writing was obtained from each patient before the start of the studies. The project was passed by the ethical practices subcommittees of both the Royal Free and the Brompton Hospitals and by the Administration of Radioactive Substances Advisory Committee.

Radioactive carbenicillin aerosols were prepared by adding to 1 g carbenicillin powder (Pyopen, Beechams) 4 ml diethylenetriaminepenta-acetic acid (DTPA) solution labelled with 185 MBq (5 mCi)

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technetium-99m. Aerosols generated from this mixture contain drug and radiolabel, so that the distribution of radiolabel in the respiratory tract reflects that of the drug.¹²⁻¹⁴

Aerosols were generated by two combinations of nebuliser and compressor. A Turret nebuliser (Medic-Aid Ltd, Pagham) coupled to a Maxi Mark I compressor (Medix Ltd, Calthorpe) was used to generate an aerosol with a mass median diameter 3.2 (0.2) μm (mean (SEM), $n = 8$) in which 71.2% (2.1%) of the aerosol mass was contained in droplets under 5 μm diameter. By contrast, an Inspiron Mini-neb nebuliser (Bard International Ltd, Sunderland) coupled to a Traveller compressor (Medix Ltd) was used to make an aerosol with an MMD of 7.3 (0.3) μm ($n = 8$) in which only 29.0% (2.5%) of the aerosol mass was contained in droplets under 5 μm diameter. Droplet sizes, measured by a Malvern Instruments 2600HSD laser particle and droplet analyser,¹⁵ were similar to those obtained when carbenicillin is diluted with sterile water for injection according to usual clinical practice.⁹ The flow rates generated by the Maxi and Traveller compressors through their respective nebulisers were 9 and 6 l/min. The Inspiron nebuliser was connected to a one way valve system (Ambu-Valve, Tricomed, London), the outlet from which led to a low resistance filter (Inspiron 002290) so that no aerosol was vented into the room; the Turret nebuliser incorporated a built in valve system. Each patient used a different nebuliser to prevent cross contamination and nebulisers, valves, and tubing were sterilised after each experiment.

Radioaerosol studies were performed on three separate days in a randomised order as follows: (1) Inspiron nebuliser plus Traveller compressor with tidal breathing (7.3 μm aerosol); (2) Turret nebuliser plus Maxi compressor with tidal breathing (3.2 μm aerosol); (3) Turret nebuliser plus Maxi compressor with a combination of tidal and deep breathing (3.2 μm aerosol). In the third study patients were instructed to take alternately four tidal breaths and four deep breaths of 1.0-1.5 l in volume. Inhaled volume, breathing frequency, and minute ventilation were determined by respiratory inductive plethysmography (Respirace Corporation, Ardsley, New York) which was used to monitor the inhalation manoeuvres as described.¹⁶ To provide a rough check on the inhaled volume while aerosol was being inhaled, the air inlet to the nebuliser was connected to a Voldyne incentive spirometer (Cheeseborough Ponds Inc, Greenwich, Connecticut). Patients inhaled aerosol for two minutes via a mouthpiece with the body of the nebuliser shielded by a lead screen. Inhalations were preceded by 10 minutes' chest physiotherapy (forced expiration technique¹⁷) to clear loose secretions from the lungs. Forced expiratory

volume in one second (FEV_1) was assessed immediately before aerosol inhalation by spirometry (Vitalograph), and maximum expiratory flow rate at 75% of the forced vital capacity ($\dot{V}_{\text{max}_{25}}$) from an Ohio spirometer coupled to an x - y plotter.

A posterior-anterior scan of radioaerosol in the chest and stomach was performed with a General Electric 400T large field of view gamma camera, starting within 60 seconds of the end of nebulisation. Counting times were 100-200 seconds and at least 40 000 counts were collected. Aerosol located in the oropharynx was then determined from a right lateral view of the head. The gamma camera was connected on line to a Nodcrest V77 600 computer, which was used to define "regions of interest" on the scans around the lungs, stomach, and oropharynx. The chest count was corrected for the patient's chest thickness according to the attenuation equations of Fleming.¹⁸ Counts emanating from the stomach during scans were assumed to have arisen from aerosol initially deposited in the oropharynx and subsequently swallowed. The total amount of carbenicillin initially deposited in the lungs and oropharynx was determined by comparing the counts obtained with those from a lung "phantom" similar in design to the models described previously.^{19,20} The phantom consisted of a 25 cm diameter hollow perspex disc 3 cm thick, filled with a known amount of the "labelled" carbenicillin (about 5 mg). The perspex disc was mounted in a wooden frame and positioned 10 cm from a 1 cm thick slab of tissue equivalent material to simulate the chest wall. The 10 cm air gap represented air in the lungs and the perspex disc activity in mid thorax. For scanning the phantom was placed in front of the gamma camera with the tissue equivalent slab in contact with the surface of the collimator.

Each patient had a krypton-81m ventilation scan, after one of the radioaerosol studies, inhaling the radioactive gas from a generator (the Medical Research Council cyclotron). The 20% contour of the ^{81m}Kr scan was then superimposed on the aerosol images and used to define the lung edge. Radioaerosol counts in three further lung zones (central, intermediate, and peripheral—fig 1) were determined from three "regions of interest" as described by Agnew *et al.*²¹ An aerosol penetration index was defined as the ratio of peripheral zone counts to central zone counts, averaged for the two lungs.

The data were not assumed to be normally distributed. Statistical significance was assessed by the Wilcoxon rank sum test for paired data.²²

Results

EFFECT OF NEBULISER SYSTEM

One patient failed to complete the trial for personal

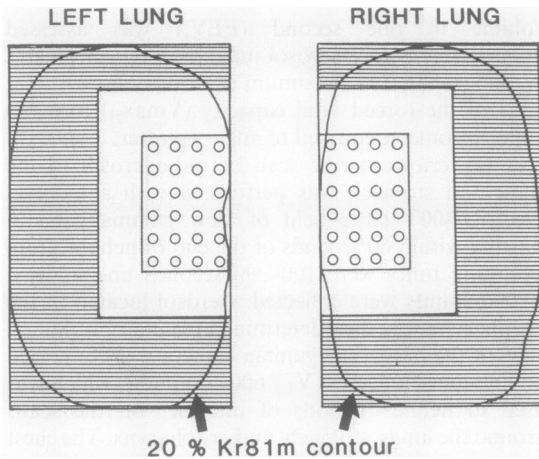


Fig 1 Aerosol distribution within the lungs. The 20% contour of the krypton-81m ventilation scan is superimposed on the aerosol image and a 5×8 matrix is fitted to this contour for each lung. Peripheral (cross hatched), intermediate, and central (stippled) regions are defined as shown.

reasons. The mean (SEM) amount of carbenicillin reaching the lungs in the other six patients was 6.54 (1.09) mg with the Inspiron plus Traveller (fig 2). Deposition was significantly greater at 15.60 (1.5) mg with the Turret nebuliser plus Maxi compressor ($p < 0.05$). Peripheral zone deposition was less (2.84 (0.44) mg) with the Inspiron nebuliser plus Traveller compressor than with the Turret nebuliser plus Maxi compressor (7.92 (0.81) mg; $p < 0.05$). The aerosol penetration index was increased from 1.38 (0.16) with the Inspiron nebuliser compared with 2.00 (0.22) with the Turret nebuliser ($p < 0.05$).

There was a trend towards higher oropharyngeal deposition with the Inspiron (9.55 (4.08) mg) than with the Turret nebuliser (4.93 (1.19) mg), but this was not significant.

Typical scans comparing the deposition patterns for the two nebuliser systems are shown in figure 3.

EFFECT OF BREATHING PATTERN

Alternate tidal and deep breathing of the $3.2 \mu\text{m}$ aerosol from the Turret nebuliser increased lung deposition in five of the six patients who completed the trial, but overall the rise from 15.60 (1.50) mg to 19.17 (2.06) mg was not significant. Similarly, the peripheral zone depositions (7.92 (0.81) mg v 9.45 (1.06) mg), aerosol penetration indices (2.00 (0.22) v 1.76 (0.08)), and oropharyngeal deposition (4.93 (1.19) mg v 5.47 (1.71) mg) did not differ significantly for the two breathing modes.

The patient who withdrew from the study had inhaled only the $3.2 \mu\text{m}$ aerosol by tidal breathing. In this case only 1.84 mg carbenicillin was deposited in

the lungs, compared with a mean of 15.6 mg in the remaining six patients. When he returned to the laboratory it was apparent that he drew aerosol into his mouth via the mouthpiece but inhaled through his nose. A repeat study was performed with the patient wearing a noseclip and the mass of carbenicillin in the lungs rose almost threefold to 4.85 mg.

LUNG FUNCTION AND INHALATION MANOEUVRES
Lung function, inhalation volumes and breathing frequencies were similar on each study day (table 1). With alternate tidal and deep breathing, minute ventilation increased compared to tidal breathing alone ($p < 0.05$).

Discussion

Deposition of carbenicillin was determined by mixing the $^{99\text{m}}\text{Tc}$ and drug solution within the nebulisers rather than by labelling the drug with the radionuclide chemically. Droplets released subsequently are assumed to contain drug and radiolabel in the same proportions as in the nebuliser reservoir, so that the distribution of radioaerosol in the lungs and oropharynx reflects that of the drug. The validity of this assumption has been discussed by Dashe *et al*¹² and by Ruffin *et al*,¹³ and the technique has been used to quantify the deposition of bronchodilators,^{12,13,23} histamine,²⁰ and gentamicin.¹⁴ The radionuclide was labelled to DTPA, since the rate of absorption of this substance through the lungs^{24,25} is sufficiently slow for scanning to be completed before there is appreciable

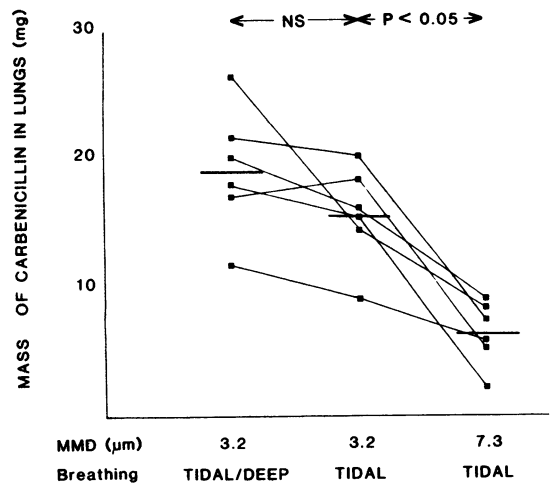


Fig 2 Mass of carbenicillin (mg) deposited in the lungs in six patients for two nebuliser systems—Turret nebuliser plus Maxi compressor (droplet mass median diameter (MMD) $3.2 \mu\text{m}$) and Inspiron nebuliser plus Traveller compressor (MMD $7.3 \mu\text{m}$) and for two breathing patterns with the Turret-Maxi nebuliser system.

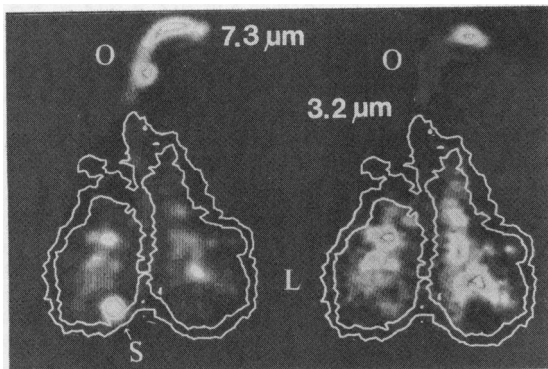


Fig 3 Typical deposition patterns with the Inspiron nebuliser plus Traveller compressor (droplet mass median diameter (MMD) 7.3 μm) and the Turret nebuliser plus Maxi compressor (droplet MMD 3.2 μm) in one patient with cystic fibrosis. The 10% and 20% contours of the krypton-81m ventilation scan are shown. O, oropharynx; L, lungs; S, stomach. The views are posterior-anterior.

loss of tracer from the field of view; inhalation was restricted to two minutes to further minimise the effects of absorption of the radiotracer. The radiation dose to the lungs has been estimated as 200 μGy (20 mrad), which is about half that from a chest radiograph.²⁶

The deposition data indicate that the amount of antibiotic aerosol delivered to the patient's lungs may be influenced dramatically by choice of nebuliser system, as predicted from *in vitro* studies.⁸⁻¹⁰ During two minutes' nebulisation more drug was delivered to the patient from the Turret nebuliser with the Maxi compressor (20.5 mg in lungs plus oropharynx) than from the Inspiron nebuliser plus Traveller compressor (16.1 mg), presumably because the Turret was driven at a higher compressed gas flow rate. With the Turret nebuliser plus Maxi compressor 76% of the aerosol reaching the patient was deposited in the lungs, compared with 41% for the Inspiron nebuliser plus

Details of lung function and inhalation manoeuvres (mean (SEM) values) for the six patients who completed all three studies.

Nebuliser system	TU + MA	TU + MA	IN + TR
MMD (μm)	3.2	3.2	7.3
Breathing pattern	Tidal + deep	Tidal	Tidal
FEV ₁ (l)	1.37 (0.13)	1.38 (0.14)	1.41 (0.12)
$\dot{V}_{\text{max}_{25}}$ (l/s)	0.26 (0.05)	0.28 (0.05)	0.30 (0.02)
Tidal breath (l)	0.77 (0.10)	0.74 (0.08)	0.82 (0.05)
Deep breath (l)	1.34 (0.15)	—	—
Breaths/minute	18.3 (2.8)	18.0 (0.9)	19.5 (2.7)
Minute ventilation (l)	18.6 (3.4)	13.4 (1.7)	16.1 (2.8)

MMD, mass median diameter; $\dot{V}_{\text{max}_{25}}$, maximum expiratory flow rate at 75% of the forced vital capacity; TU, Turret nebuliser; IN, Inspiron nebuliser; TR, Traveller compressor; MA, Maxi compressor.

Traveller compressor, the difference presumably being due to the smaller droplet MMD from the Turret nebuliser. Different combinations of nebulisers and compressors produce droplets with widely differing size distributions⁹ and droplets smaller than 5 μm diameter are said to constitute the "respirable range."²⁷ Some nebuliser systems may be ineffective because they are unable to deliver the dose to the required site of action in sufficient quantity. The droplets of smaller size also penetrated better to the peripheral zone of the lungs, which suggests enhanced aerosol delivery to the smaller conducting airways; the required site of deposition of antibiotic aerosols within the bronchial tree is, however, poorly understood. As noted in earlier studies,^{19,24,28,29} only a small percentage of the drug dose in a nebuliser actually reaches the lungs. With nebulisation for a fixed time rather than to dryness the difference between the two nebuliser systems was accentuated, and it would be possible to compensate for this by increasing the delivery time with the Inspiron-Traveller system. Nebulisation of a full treatment dose to dryness, however, takes more than 30 minutes for the relatively weak Traveller compressor,⁹ and many patients will be unwilling or unable to comply with treatment of this duration.

The addition of deep breathing to normal tidal breathing for the 3.2 μm aerosol caused a small increase in deposition, but the additional respiratory effort required is probably not justified in terms of improved drug delivery. The increased volume inhaled during deep breathing should have carried aerosol to more peripheral lung regions.³⁰ Patients maintained the same breathing rate, however, while taking deep breaths, indicating that these were inhaled relatively rapidly. This would tend to deposit aerosol centrally,³⁰ thus countering the effect of inhaling deeply, and this may explain the similar aerosol distributions for the two breathing modes. Attention to inhalation technique may be important, however. The low deposition in the patient who inhaled through the nose while receiving the aerosol via a mouthpiece suggests that some patients may be using their nebulisers incorrectly and may consequently derive little therapeutic benefit. The use of a noseclip or facemask should help to eliminate simple errors of this type, and could usefully be considered in patients who are not deriving the expected benefit from treatment.

The nebuliser systems tested in this study may have represented opposite extremes so far as droplet mass median diameters are concerned; most other systems probably have an MMD in the range 3–7 μm .⁹ Large droplet sizes are sometimes, but not always, associated with relatively weak "portable" brands of compressor. Droplet MMD varies inversely with the pressure or flow rate generated by a compressor, but it also depends on the type of nebuliser. *In vitro* studies have

shown that the weaker compressors are often unsatisfactory because of the time taken to nebulise a standard dose of carbenicillin⁹; this study indicates that weaker compressors may also be unsatisfactory because they lead to the generation of larger aerosol droplets, fewer of which reach the lungs. A relatively powerful compressor, coupled to a nebuliser with a droplet MMD of less than 5 μm , is thus the system of choice for antibiotic aerosol treatment.

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