

PERSONAL PRACTICE

Aerosol antibiotic treatment in cystic fibrosis

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The outlook for people with cystic fibrosis has improved steadily since the first description of the disease in the late 1930s. A major reason for the improved prognosis has been the availability and effective use of antibiotics to delay the onset, and slow the progress, of the inevitable bronchopulmonary bacterial colonisation and infection that will eventually prove fatal.

During the 1970s and 1980s the main emphasis of treatment concerned intravenous antibiotics as techniques of intravenous access had improved. Also, more patients survived to become infected by *Pseudomonas aeruginosa* for which only intravenous antibiotics were effective until the recent introduction of the quinolones (for example, ciprofloxacin). However, during this period there appeared sporadic reports of the use of aerosol antibiotics. In 1981, a controlled study comparing twice daily nebulised gentamicin 80 mg and carbenicillin 1 g with placebo demonstrated a slowing of the decline of respiratory function tests between courses of intravenous antibiotic treatment.¹ In patients recently colonised by *P. aeruginosa*, nebulised colistin sulphomethate reduced the frequency of cultures positive for the organism.²

Although some reports of the use of aerosol antibiotics have been anecdotal and uncontrolled, the majority have reported that patients benefited from their use. Controlled studies have confirmed benefit to the patients in the treated groups.^{1,3,4}

During the past five years there has been a steady increase in the use of aerosol antibiotics in a variety of clinical situations. Attitudes to the early treatment and control of pseudomonas infection in patients with cystic fibrosis have changed, with an impatience to eradicate *P. aeruginosa* at an early stage after colonisation, rather than waiting until tissue infection is well established⁵ (C Vasquez *et al*, European Cystic Fibrosis Conference, 1991).

The discovery of the cystic fibrosis gene and consequent new treatment possibilities have increased the interest in early treatment and the prevention of pulmonary damage. Many clinicians are now prepared to recommend more time consuming treatment regimens for patients who are relatively well in an attempt to maintain the patient in as good a condition as possible so that maximum benefit may be available subsequently.

The importance of the method of delivery of the aerosol antibiotics has been emphasised by a number of workers.⁶⁻⁹ However, it is still common for those with cystic fibrosis to be

prescribed nebulised antibiotics using an inappropriate nebuliser and inadequate compressor system often using a mask when a mouthpiece would have been more appropriate. These patients are wasting a great deal of time and deriving little or no benefit from a potentially valuable type of treatment. Many useful data have been published over the past decade on the techniques and equipment for efficient nebulisation of antibiotics but some has appeared in journals not usually read by general paediatricians. The purpose of this article is to review the clinical indications, drugs used, and methods of administration of inhaled antibiotics in cystic fibrosis.

Clinical indications

● *To maintain the present state of the patient or reduce the speed of decline.*^{1,4,5,10,11} The first controlled trial on the use of aerosol antibiotics compared the effect of 80 mg of gentamicin and 1 g of carbenicillin aerosol twice daily and placebo on the rate of deterioration and frequency of hospitalisation in adults.¹ The treated group fared significantly better. In a later study ceftazidime was also effectively used in this way.¹² A similar advantage in reducing the decline of respiratory function between courses of intravenous antibiotics was demonstrated in a study using nebulised colistin sulphomethate.⁴

● *As additional treatment to enhance the effect of intravenous antipseudomonas antibiotics.* The controlled studies that have been performed have failed to show any advantage from adding an aerosol antibiotic to a standard course of intravenous antibiotics.^{13,14} Thus, although in one controlled study the addition of nebulised amikacin (100 mg twice a day) to amikacin and ceftazidime did lead to greater short term eradication of the pseudomonas, there was no long term benefit.¹⁴

● *To treat acute episodes of infection.* Although not usually used for acute treatment, 80 mg of tobramycin and 1 g carbenicillin nebulised twice daily were considered to be as effective as intravenous treatment.¹⁵ Nebulised tobramycin 80 mg 'two or three times daily' was also considered effective in an uncontrolled evaluation of treatment of acute exacerbations.¹⁶

● *To treat early colonisation with *P. aeruginosa*.*^{2,5} Our initial early experience with the use of inhaled colistin sulphomethate in early colonised patients demonstrated a significant reduction in positive cultures for *P. aeruginosa* after the start of regular aerosol colistin sulphomethate.² The use

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of inhaled and oral antipseudomonal antibiotics appears to be very effective in eradicating pseudomonas soon after initial colonisation⁵ (C Vasquez *et al*, European Cystic Fibrosis Conference, 1991).

● *Prevention of pseudomonas colonisation.* In view of the inevitable occurrence of bacterial colonisation and infection of the respiratory tract, aerosol antibiotic prophylaxis from the time of diagnosis has been recommended by some clinics (San Diego Experience, Perspectives in Cystic Fibrosis, 1980). The use of regular aerosol aminoglycosides from infancy has been associated with a reduction in respiratory symptoms (M Zach 1992, personal communication). This is probably a particularly important area as evidence is accumulating indicating that it is easier to prevent *P aeruginosa* colonising the respiratory tract than to eradicate the organism once established.¹⁷

Antibiotics used in aerosol administration

In the 1950s and 1960s neomycin and subsequently methicillin, were used as aerosols against *Staphylococcus aureus*. Many other antibiotics have been used for aerosol treatment in cystic fibrosis patients but more recently antibiotics active against *P aeruginosa* have attracted the most interest. The majority of studies have been with aminoglycosides, in particular gentamicin and tobramycin. Aminoglycosides have good antipseudomonal activity, but when administered systemically have poor penetration of bronchial secretions, with concentrations being well below the minimum inhibitory concentration of the infecting organism.¹⁸ Although not cheap, the aminoglycosides represent one of the least expensive classes of antipseudomonal treatment. The more common aminoglycosides are a liquid formulation and therefore do not require reconstitution.

Gentamicin is the cheapest in the group, but our experience suggests resistance is increasingly becoming more of a problem. It has better activity than tobramycin against *S aureus* (Jenkins *et al*, Cystic Fibrosis Club Extracts 1985; 26, 147).

Tobramycin has a very similar antimicrobial activity to gentamicin but has increased intrinsic activity against *P aeruginosa*, resistance is less of a problem, and it is less nephrotoxic.¹⁹⁻²²

Amikacin has been used more recently¹⁴ but fewer studies have been reported. Its use could prove useful when bacterial resistance to the other aminoglycosides occurs.

Colistin sulphomethate is a polymixin antibiotic, derived from the spore bearing soil bacillus. It has good antipseudomonas activity but has no Gram positive activity. Resistance is not readily acquired, probably helped by its infrequent systemic use. These characteristics make colistin sulphomethate a good first line choice against *P aeruginosa*. However, *Pseudomonas cepacia* is colistin sulphomethate resistant and there are suggestions that treatment with colistin sulphomethate may lead to superinfection with colistin sulphomethate resistant organisms, such as *P cepacia*.²³ This is not our experience.²⁴

Ceftazidime, a third generation cephalosporin, has also been used.¹² The third generation cephalosporins have good antipseudomonal and *Haemophilus influenzae* activity but poor staphylococcal activity. Ceftazidime is, however, expensive.

Only a few studies on the use of aerosol penicillin treatment have been reported. Carbenicillin and ticarcillin have been used in conjunction with an aminoglycoside.¹²⁵ Cephaloridine and cloxacillin have also been used.²⁶

Amphotericin is an antifungal agent that has found a place as prophylaxis against invasive aspergillosis, in its nebulised form. Patients with cystic fibrosis sometimes have allergic bronchopulmonary aspergillosis and antifungal treatment may be necessary before and after transplant. In the nebulised form amphotericin can be given at home for long periods.²⁷⁻²⁹

SIDE EFFECTS

● *Bacterial resistance as a result of exposure to low concentrations of the inhaled antibiotic.* A number of studies have reported some increase in resistance strains after inhaling aminoglycosides for prolonged periods but the proportion which show serious resistance is relatively small.¹ The clinical efficacy surprisingly does not appear to correlate with the bacterial sensitivity of the organism.³⁰ Even giving aerosol antibiotics from the time of diagnosis does not appear to be associated with significant bacterial resistance.

● *Selection of particularly difficult organisms, for example P cepacia.* *P cepacia* is resistant to colistin sulphomethate and as already discussed there is a theoretical possibility that it may be selected out if colistin sulphomethate was inhaled for prolonged periods. This has not been our experience.²⁴ However, the possibility of selection of multiply resistant organisms should be considered and further evaluated.

● *Local irritation.* Aerosol antibiotics may cause cough and bronchospasm. The osmolality of the solution appears to be an important factor and hypertonic solutions are more likely to cause problems. The fall in respiratory function is greater after ticarcillin (osmolality 3080 mosmol/kg) than saline (272 mosmol/kg) and tobramycin (248 mosmol/kg).²⁵ By comparison, the osmolality of colistin sulphate is 297 mosmol/kg. *It is important that respiratory function tests are performed before and after a dose of the aerosol antibiotic to assess the significance of any irritation.*

● *Allergies in staff and relatives.* This should be considered, although there appear to be no reports of such occurrences.

Methods of administration

In any discussion of the use of nebulised antibiotics it is essential to give adequate details of the techniques used to generate and deliver the aerosol. Use of a poor technique (for example a weak compressor or nasal inhalation) will lead to greatly reduced pulmonary deposition and unsatisfactory clinical results.^{31 32}

Aerosols for medical use may be generated by ultrasonic or jet nebulisers. Previous work has

assessed the comparative performance of a jet and an ultrasonic nebuliser³³ and suggests that the ultrasonic nebuliser may be unsuitable for applications requiring high yields of fine particles for delivery to the peripheral lung regions. Larger volumes of drug solution are required than for a jet nebuliser.³⁴ Much of the electrical energy required to operate an ultrasonic nebuliser is converted into heat, thereby raising the temperature of the drug solution.³⁵ The effect of the temperature increase on the antibiotics is unclear but many common applications of aerosol antibiotics employ jet nebulisers, although ultrasonic nebulisers continue to be developed. The remaining discussion will refer exclusively to jet nebulisers.

In optimising the aerosol generation and delivery system for clinical use, attention must be given to three aspects of technique: (i) formulation of the drug solution or suspension, (ii) selection of an appropriate nebuliser and compressor, and (iii) effective inhalation by the patient. Each of these areas will now be reviewed in more detail.

(i) ANTIBIOTIC FORMULATION

Antibiotics are commonly produced as a drug powder that may then be diluted using an appropriate diluent to form a solution or suspension of the drug. Care must be taken to ensure that if the drug forms a suspension in the diluent, the droplet size of the aerosol produced by the jet nebuliser is greater than the size of the antibiotic particles in suspension. This will ensure that the aerosol can be an effective carrier of the drug. During the nebulisation process, evaporation of the diluent will occur and this will increase the concentration of drug remaining in the nebuliser reservoir.³⁶ For a given mass of drug, the amount of drug delivered as respirable aerosol will be increased by increasing the volume of diluent used.^{31, 37} Small volumes of diluent lead to significant reduction in the efficacy of nebulisation as the nebuliser has a residual or 'dead' volume of solution that will remain in the nebuliser at the end of nebulisation and which may represent up to 50% of the original volume for 2 ml of drug solution.⁹ A volume of 4 ml drug solution^{9, 31, 38} is suggested as a compromise between a long nebulisation time and efficient nebulisation.

Antibiotic solutions and suspensions have a range of surface tensions and viscosities. The residual volume increases, and hence mass of respirable aerosol release decreases, as the surface tension increases.^{9, 39} However, the effect of the surface tension and viscosity on the size of the particles released by the nebuliser for inhalation may not be readily predicted.⁴⁰

(ii) SELECTION OF APPROPRIATE NEBULISER AND COMPRESSOR

There is a large number of jet nebuliser and compressor combinations available and the choice of an effective combination is critical to the delivery of adequate amounts of drug aerosol.

The nebuliser should have a small residual volume in order to maximise the mass of drug

released as respirable aerosol and reduce the amount of solution retained on the internal baffles and walls of the nebulisers. The residual volume varies widely between nebulisers,³¹ but decreases as a proportion of the original solution volume for larger initial volumes.^{9, 31} It is suggested that an efficient nebuliser should have a residual volume not exceeding 0.8 ml for an initial volume of solution of 4 ml.

The nebuliser must also produce the majority of its aerosol output in the respirable particle diameter range 0.5 μm – 5 μm .⁴¹ This is affected by the design of the nebuliser and the compressor air flow rate.^{31, 42, 43} As the larger diameter particles have greater mass it is important that the mass of the drug released in particles less than 5 μm in size is specified. It is, therefore, useful to specify the mass median diameter for the distribution (that is, the diameter that divides the size distribution into two equal halves by mass). Mass median diameters should be in the range 3–5 μm .^{38, 42} The size of the particles may change due to evaporation or droplet growth in the saturated vapour which will exist in the airways. These effects are more difficult to estimate but the smaller the particle the more readily it will penetrate to the alveolar region of the lung while very small droplets (less than 1 μm in size) may be exhaled.⁴¹

In order to ensure a small particle size the compressor flow rate should be greater than 10 litres/min.^{31, 42, 44} This flow rate should represent the flow through the nebuliser chamber³⁸ as the flow measured directly from the compressor in the absence of the nebuliser will be higher than that achieved when the nebuliser is in line with the compressor. A high flow rate also reduces the nebulisation time³¹ and 10–20 minutes is suggested as a clinically acceptable range. This is consistent with a minimum gravimetric output from the nebuliser of 0.2 ml/min. Larger droplet sizes are associated with the weaker, portable compressors and the use of domiciliary oxygen cylinders operating at lower flow rates (typically 4 litres/min maximum). Some nebulisers employ a Venturi effect, which results from the patient inhaling, to increase the output of the nebuliser but this effect may be nullified by inclusion of the additional filtration and valve system often required by antibiotic nebulisers to prevent the release of antibiotic to the environment. The inclusion of an aerosol trapping device has also been shown to reduce antibiotic wastage during exhalation.⁴⁵

Evaporative losses of diluent lead to an increasing concentration of drug in the solution remaining in the nebuliser.^{36, 37} Also the nebuliser output is initially continuous but will eventually become intermittent and drug output will then decrease significantly.^{46, 47} It is important to maximise nebuliser output (by tilting or gentle shaking) during the later stages of nebulisation as drug output is maximum during this phase.³⁷

(iii) BREATHING TECHNIQUES

Nasal inhalation of an aerosol results in insignificant pulmonary deposition of the aerosol.⁴³ Inhalation must occur using the mouth only and an ideal combination is to use a mouthpiece with

nose clip, while facemasks must be used as an aid to oral inhalation only. An appropriate breathing technique may assist in increasing alveolar deposition and should comprise an initial deep, slow, inhalation followed by a short breath hold and more rapid exhalation.⁴⁸ Tidal volume and aerosol concentration influence the rate at which the drug is delivered.⁶ Thus, at low tidal volumes the rate of drug delivery increases with tidal volume and aerosol concentration. At higher tidal volumes the drug delivery rate depends on aerosol concentration and volume, and is independent of tidal volume. This is because at higher tidal volumes peak inspiratory flow exceeds the gas flow through the nebuliser, air entrainment occurs and the concentration of aerosol decreases. Thus little additional drug is inhaled.^{6,49}

Overall it is likely that up to 10% (by mass) of the drug will be deposited in the lung.⁵⁰

FURTHER DEVELOPMENTS

More recent work has studied the use of a Rotahaler (Allen and Hanburys) to deliver micronised gentamicin powder.⁵¹ Lung delivery was compared with that achieved using a jet nebuliser and similar levels of gentamicin were detected in bronchoalveolar lavage fluid, although the micronised gentamicin powder caused cough in half the patients. If this problem could be overcome it may be a convenient alternative to jet nebuliser use. Improved quality control and manufacturing techniques are likely to reduce variation in performance between nebulisers, recently demonstrated as a significant problem.⁵² Improved understanding by the user of the importance of a good quality nebuliser system, rather than simply the cheapest, will encourage the production of good quality systems.

Nebuliser practice at the Regional Cystic Fibrosis Unit, St James's University Hospital

Nebulised antibiotics are usually reserved for home use as there appears to be no benefit in adding inhaled antibiotics to systemic therapy.^{13,14} Before patients are prescribed inhaled antibiotics, they are given a 'test dose' under supervision. The appropriate antibiotic is chosen on the basis of microbial sensitivities and the dosage details are given in the table. Respiratory function tests are performed before and after administration of the nebulised drug to check for any adverse effects, such as bronchospasm. If the patient needs to have nebulised antibiotics while in hospital, or for the test dose, the patient is removed from the ward and given the dose in a side room with the exhaled breath going via a tube into a fume cupboard. Nebulising antibiotics on the ward could lead to resistant micro-organisms.

A nebulised β_2 agonist (salbutamol) is given before physiotherapy and the antibiotic is given after physiotherapy. If absolutely necessary, the bronchodilator may be added to the antibiotic, having checked that the combination is admissible. This is a useful way of overcoming bronchospasm difficulties if nebulised antibiotic

Dosages of nebulised antibiotics used at the Regional Cystic Fibrosis Unit, St James's University Hospital

Drug	Age (years)	Dose (mg)	Frequency (per day)
Tobramycin	<2	40	2
	>2	80	2
	>12	160	2
Gentamicin	<2	40	2
	>2	80	2
	>12	160	2
Colistin sulphomethate	<6	0.5*	2
	>6	1.0*	2
	>12	500	2
Amikacin	>12	500	2
	<12	250	2
Amphotericin		10	2-4

*Dose in megaunits.

treatment is considered essential. Antibiotics are always nebulised using a powerful compressor such as a Maxi III or Turboneb compressors (Medix Ltd), with a System 22 and Acorn nebuliser system (Medicaid Ltd). The solutions are routinely made to a 4 ml volume using 0.9% saline. Water can cause bronchospasm and is therefore not used except with amphotericin, which precipitates with saline.

Conclusions

The delivery of antibiotics as an aerosol to the lungs of patients with cystic fibrosis has become an increasingly popular and effective approach to the prevention and treatment of pulmonary infection. This interest is likely to increase further with the possibility of new treatment methods that arise after the discovery of the cystic fibrosis gene. A considerable amount of clinical evidence suggests that it is an effective method of treatment when appropriate antibiotics are administered effectively at an early stage. An increasing number of antibiotics are available for nebulisation and, as experience is gained, it seems that systemic toxicity and bacterial resistance are not significant problems. The advantages and clinical benefits of nebulised antibiotics outweigh any minor disadvantages.

When using jet nebulisers, however, effective aerosol administration is critically dependant upon using an adequate volume of drug solution in an efficient nebuliser that will generate aerosol particles in the 1-5 μm range, using a sufficiently high gas flow in conjunction with an effective inhalation technique. Advances in delivery technology should give significant improvements in patient management and the use of nebulised antibiotics continues to hold promise in the management of infection in cystic fibrosis.

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