Nebulised antibiotics for adults with cystic fibrosis

A K Webb, M E Dodd

During adolescence most patients with cystic fibrosis become chronically colonised with Pseudomonas aeruginosa. Acquisition of this organism is associated with a worse prognosis. The emphasis of care is to delay the progression of pulmonary sepsis which is responsible for almost the total mortality of patients with cystic fibrosis. Repeated sputum culture of P aeruginosa confirms chronic infection and it is then impossible to eradicate. Regular courses of intravenous antibiotics have improved survival by reducing sputum load and maintaining pulmonary function, but they interfere with the activities of daily living. The prescription of nebulised antibiotics for domiciliary use by patients with cystic fibrosis is increasing. However, experienced physicians working in cystic fibrosis centres have shown considerable variability in their prescribing practices.

Clinical indications

DELAY OR PREVENTION OF CHRONIC COLONISATION WITH P. AERUGINOSA

The introduction of nebulised colistin at the time of initial colonisation with P aeruginosa may reduce and delay chronic colonisation, defined as three consecutive positive sputum cultures within six months. In an uncontrolled trial nebulised colistin given to seven children with cystic fibrosis reduced the frequency of positive cultures from 40% to 0%. In a controlled prospective study a combination of nebulised colistin and oral ciprofloxacin significantly prevented or delayed chronic infection with P aeruginosa for 18 months. These results suggest a role for nebulised antibiotics when the organism is first isolated from sputum. No trials have been published on the use of nebulised antibiotics at the time of diagnosis of cystic fibrosis before P aeruginosa has been cultured from the sputum.

PREVENTION OF CLINICAL DETERIORATION IN PATIENTS CHRONICALLY INFECTED WITH P. AERUGINOSA

Regular aerosolised antibiotics have been used for patients chronically infected with P aeruginosa to reduce the rate of deterioration. An early controlled trial compared twice daily administration of 80 mg nebulised gentamicin combined with 1 g carbenicillin against placebo. In the group that received the active drugs for six months there was a reduction in hospital admissions for infective exacerbations and pulmonary function was maintained. Aerosolised therapy was cost effective because of the reduced hospital costs.

Ceftazidime was compared with a combination of gentamicin with carbenicillin in a crossover study in which saline was used as the placebo. Each arm of the crossover period lasted for four months. Both active drug regimens were equally effective in increasing body weight and improving lung function compared with placebo. These results suggest that only nebulised antibiotic is required for efficacy.

A recent short term study recruited 71 patients into a controlled trial of placebo versus high dose nebulised tobramycin, 600 mg/day. The high dose of tobramycin was used to increase the bactericidal dose of antibiotic in the sputum against tobramycin sensitive P aeruginosa. There was a significant improvement in pulmonary function and a reduction of P aeruginosa in the sputum. Bacterial resistance patterns were similar during the active and placebo part of the study. No ototoxicity or nephrotoxicity was observed. These results suggest that high dose nebulised tobramycin is clinically effective, safe, and does not promote bacterial resistance.

Nebulised tobramycin, 80 mg twice daily, was evaluated in a long term open study (mean duration 20 months) in 14 patients with a mean age of 13.3 years. Clinical parameters improved and hospital admissions decreased. There was a reduction in one or more inflammatory markers (antibody serum titres to P aeruginosa, elastase, exotoxin A, alkaline phosphatase) in eight patients. No tobramycin was detected in 50 of 70 blood samples. Intermittent tobramycin resistance developed in five patients (but only in 6.2% of strains) and persisted in only one patient at the end of the study. These results suggest that long term nebulised aminoglycosides are safe, clinically effective and, by reducing the bacterial antigen load, may diminish the systemic host immune response.

A review of five randomised controlled trials showed benefit for nebulised antipseudomonal antibiotic therapy with no demonstrable adverse effects. There is no evidence to suggest that nebulised antibiotics used as an adjunct to a course of intravenous antibiotics augment clinical improvement. Nebulised antibiotics should not be used as an alternative to intravenous antibiotics for an infective exacerbation.

Assessment and administration

PATIENT ASSESSMENT

Patients should be carefully assessed before treatment with nebulised antibiotics is started.

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A recent sputum culture should be used to determine which antibiotic to prescribe according to resistance patterns. Colistin is infrequently used intravenously and resistance to *P. aeruginosa* is uncommon. Each patient should be given a hospital supervised dose after chest physiotherapy and spirometric tests should be performed before and immediately after challenge. Maximal bronchoconstriction to nebulised antibiotics usually occurs immediately after administration. Bronchoconstriction is usually related to hypertonicity of the antibiotic solution. Prevention of bronchoconstriction may be achieved by altering the tonicity by dilution with water or half normal saline.

It is recommended that patients use nebulised antibiotics after physiotherapy and bronchodilators to ensure maximum deposition and protection from bronchoconstriction. Patients should be provided with a mouthpiece rather than a face mask to maximise pulmonary deposition. Relaxed tidal volume breathing through the mouth and not the nose is recommended for patients using nebulised antibiotics. Finally, patient compliance levels should be checked after a period of domiciliary use. Irregular usage is not recommended and is a reason for cessation.

**Distribution of Nebulised Antibiotic in the Lung**

Overall, about 10% of a nebulised drug is delivered to the lungs. A study in volunteers and five mechanically ventilated patients given 300 mg nebulised tobramycin found that 5.5% of the initial dose was excreted in the urine of both groups. A piece of normal lung tissue was removed from the ventilated patients who were undergoing thoracotomy and mean concentrations of 5.5 μg/g and 3.6 μg/g were found at four and 12 hours. Systemic absorption of nebulised aminoglycosides does occur in patients but the amount absorbed proportional to the dose delivered as measured by urinary excretion is small (0.5%).

The concentration of aerosolised antibiotic in bronchial secretions may not always achieve bactericidal levels, sublethal concentrations may diminish bacterial virulence factors.

**Choice of Antibiotic and Formulation**

The polymyxin antibiotic colistin and the aminoglycosides tobramycin and gentamicin are the most commonly prescribed nebulised antibiotics. Colistin is currently the only antibiotic licensed in the UK for inhalation. Tobramycin probably has greater activity than gentamicin against *P. aeruginosa*. Infrequently used antibiotics for nebulisation include cefoxazime, carbencillin, and ticarcillin. Colistin has excellent antipseudomonal activity and is probably the first line choice for nebulised use.

**Table 1: Commonly used nebulised antibiotics**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Daily dose</th>
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<tbody>
<tr>
<td>Colistin</td>
<td>2 mega units 12 hourly</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>80 mg 12 hourly</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>80 mg 12 hourly</td>
</tr>
</tbody>
</table>

Colistin is the only antibiotic licensed in the UK for inhalation.

Nebulised antibiotics are prescribed twice a day for domiciliary use. Drugs and dosages are presented in tables 1 and 2.

**Antibiotic Safety**

**Resistance**

Concern has been expressed that bacterial resistance will develop with the administration of sublethal twice daily doses of aerosolised antibiotics. Resistance does occur but is often intermittent and not related to clinical deterioration.

**Environmental Safety**

Concern has been expressed that the liberal use of nebulised antibiotics may be a health hazard to medical personnel and constitute a threat to the hospital and home environment. Staff caring for patients using nebulised antibiotics have experienced bronchoconstriction and cutaneous rashes. Although it has been suggested that polluting the hospital atmosphere may lead to the establishment of resistant organisms, particularly on intensive care units where patients may receive nebulised antibiotics following transplantation to maintain airways sterility, there is no published medical evidence to support this.

In hospital a nebuliser should be fitted with a high efficiency breathing filter on the expiratory port to prevent environmental contamination and patients with cystic fibrosis can usually stop their nebulised antibiotics when they are receiving intravenous antibiotics. It is advisable for patients to receive them in a separate area.

At home patients should nebulise their antibiotics in a separate room. They do not need to vent their exhaled antibiotics for safety reasons although they may wish to do so to eliminate the odour. If they have a sibling with cystic fibrosis they should use a filter.

**Table 2: Isotonic solutions of colistin**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Volume ml</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin 2 mega units</td>
<td>4 ml</td>
<td>2 ml 0.9% NaCl + 2 ml 0.9% NaCl</td>
</tr>
<tr>
<td>Colistin 2 mega units</td>
<td>2.5 ml</td>
<td>1.5 ml 0.9% NaCl + 1 ml 0.9% NaCl</td>
</tr>
<tr>
<td>Colistin 2 mega units</td>
<td>3 ml</td>
<td>2 ml 0.9% NaCl + 1 ml 0.9% NaCl</td>
</tr>
</tbody>
</table>

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Table 3: Order of preference for compressor/nebuliser systems for nebulised antibiotics

| Nebulised antibiotics for adults with cystic fibrosis | 1. Inhaled ceftazidime or tobramycin for initial or extended treatment of Pseudomonas aeruginosa infection. | 2. Inhaled colistin for initial treatment of Pseudomonas aeruginosa infection. | 3. Inhaled aminoglycosides for maintenance or secondary prophylaxis of Pseudomonas aeruginosa infection. |

**Patient safety**

The respiratory side effects of aerosolised antibiotics are mainly limited to bronchoconstriction at time of delivery. Curaneous rashes are rare but may occur with nebulised drugs. A sore mouth may be due to candidiasis and local tissue damage, although the incidence is not known. If a mask is used the face should be washed after antibiotic nebulisation.

**Antibiotic delivery**

Antibiotics are available as a solution or powder and are reconstituted as a solution using saline or water to a volume of 4 ml (2.5 ml for a 5 l/min compressor). Nebulisation should take no longer than 10 minutes in order to ensure maximum compliance. The combination of an electrical compressor and nebuliser must then be matched to maximise effective delivery of the nebulised antibiotic to the patient. The requirements of a system for nebulising antibiotics may differ from other solutions. Continuous improvements are taking place to meet patient requirements. Some recommended systems are shown in Table 3.

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