

Nebulised antibiotics

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Introduction

The advantages of nebulised antibiotic therapy for *Pseudomonas aeruginosa* infection in CF have been recognised for over 30 years (Mearns, 1970). An antibiotic delivered directly to the site of infection should be most effective. The altered lung environment consequent on inadequate CFTR protein function may reduce drug accumulation by the bacteria, and aminoglycoside efficacy may be reduced by binding to the excess extracellular neutrophil DNA (Levy *et al*, 1983). Sputum concentrations 25 times greater than the minimum inhibitory concentration (MIC) may be necessary to achieve a bactericidal effect (Mendelman *et al*, 1985). These levels cannot be reached by intravenous administration without unacceptable risks of systemic toxicity, but can be realised by inhalation of aerosolised antibiotics which, because of their minimal systemic absorption are unlikely to cause ototoxicity or nephrotoxicity (Smith *et al*, 1989).

Practicalities of administration

Patients should be assessed before and after a test dose of a nebulised antibiotic. In children chest auscultation and, where possible, respiratory function tests are performed. In adults pre and post respiratory function tests are performed. Some patients will develop bronchospasm and may benefit from bronchodilator inhalation given before the antibiotic (Dodd *et al*, 1997; Cunningham *et al*, 2001; Althman *et al*, 2002). A mouthpiece is preferable to a mask to maximise pulmonary deposition.

Nebulised antibiotics should be taken after physiotherapy to ensure maximum deposition.

Tobramycin crosses the placenta and there is a theoretical risk of damage to the VIII cranial nerve and of nephrotoxicity. Avoidance of parenteral administration is recommended during pregnancy but the risks from nebulised administration are much less. A decision whether or not to continue nebulised antibiotic treatment during pregnancy should be made on an individual basis and in consultation with the patient. The minimal but theoretical risks to the baby of continued treatment should be weighed against the risks to the mother's health of stopping treatment.

Clinical indications

- i) Delay or prevention of chronic infection with *P. aeruginosa*
- ii) Prevention of clinical deterioration in patients chronically infected with *P. aeruginosa*

Regular nebulised antibiotics reduce the rate of decline of respiratory function in patients chronically infected with *P. aeruginosa*. In 1981, Hodson *et al* compared six months of treatment with twice-daily nebulised gentamicin (80mg) and carbenicillin (1gm) versus placebo (Hodson *et al*, 1981). Treated patients had significantly improved respiratory function and a non-significant trend towards fewer hospital admissions. Follow-up studies confirmed the benefits of treatment for chronic *pseudomonas* infection; improved lung function, a slower decline in lung function, fewer hospital admissions, better clinical scores and weight, and decreased *P. aeruginosa* density and virulence factors (Conway, 1999). There was no renal toxicity, ototoxicity or increase in bacterial resistance (Touw *et al*, 1995; Mukhopadhyay *et al*, 1996).

Low systemic and high local concentrations of colistin after nebulised delivery (Ratjen *et al*, 2006), and a randomised double blind study of TOBI® (Ramsey *et al*, 1999) support their use in patients with chronic *P. aeruginosa* infection. In the TOBI® study the first cycle of treatment produced a 12% increase in FEV₁ which was maintained through the study. There was also a significant fall in colony forming units per gram of sputum, and patients required fewer intravenous antibiotic treatments. Sputum drug concentrations greater than 25 times the MIC value were seen in 95% of patients. Adolescent patients responded particularly well with 14% improvement in FEV₁ compared with 1.8% for controls (Moss,

2002). Increasing *P. aeruginosa* tobramycin resistance was not associated with reduced clinical efficacy (Ramsey *et al*, 1999). There was no increased isolation of intrinsically tobramycin resistant micro-organisms (Burns *et al*, 1999). Colistin resistance is rare (Denton *et al*, 2002; Govan, 2002), and in our experience sensitivity returns when colistin inhalation and intravenous use is suspended for six months. A comparative study of twice-daily nebulised TOBI® (300mg) and nebulised colistin (1 mega unit), at present the only antibiotics licensed in the UK for nebulisation in CF, showed that both treatments reduced the bacterial content of the sputum significantly, and FEV₁ increased by 6.7% with TOBI® and 0.37% with colistin (Hodson *et al*, 2002; Govan, 2002).

The Cochrane Review found insufficient evidence to claim superiority for either TOBI® or colistin. Eleven trials met the inclusion criteria. The review concluded that nebulised antibiotic treatment improves lung function and reduces the frequency of respiratory exacerbations. There was no evidence of clinically important adverse events (Ryan *et al*, 2003).

Long term treatment is effective with patients having fewer hospital admissions and intravenous antibiotic use, and better preservation of respiratory function (Moss, 2001). Long term treatment is generally very safe but patients show an unpredictable range of systemic antibiotic absorption. The possibility of toxic drug levels resulting from nebulised antibiotic delivery should be remembered. Acute renal failure after one week of TOBI® and concurrent ciprofloxacin, and reversible vestibular dysfunction in a patient receiving haemodialysis have been reported (Hoffmann *et al*, 2002; Edson *et al*, 2004). Following inhaled gentamicin children showed significantly raised, but reversible, urinary N-acetyl-b-D-glucosaminidase (NAG) activity indicating renal tubular damage, compared to control children who had never received inhaled gentamicin or who had discontinued the drug at least three months previously. There was a positive correlation between NAG levels and cumulative antibiotic dose (Ring *et al*, 1998).

There is no published evidence to support concern that nebulised antibiotics may be a health hazard to medical personnel or the hospital and home environment.

Some drug solutions/suspensions show physico-chemical compatibility and may be mixed in the nebuliser chamber for simultaneous inhalation (Kamin *et al*, 2006).

Acute respiratory exacerbations

There are no trials showing that nebulised antibiotics are as effective as intravenous antibiotics for treating infective exacerbations, or that they are useful adjuncts to intravenous therapy (Stephens *et al*, 1983; Schaad *et al*, 1987; Semsarian, 1990).

Nonetheless, clinicians may wish to use TOBI® for the treatment of exacerbations associated with multi-resistant *P. aeruginosa* because of the high endobronchial antibiotic levels achieved. The high sputum drug concentrations may render the usual laboratory breakpoints meaningless (Saiman *et al*, 1996; Lang *et al*, 2000).

Prevention of *P. aeruginosa* infection

Twice daily inhaled gentamicin in a small group of very young children prevented chronic infection for a mean of 78 months (Heinzl *et al*, 2002). Regular use of nebulised TOBI®, colistin, injectable forms of tobramycin or amikacin are associated with a chronic *P. aeruginosa* infection rate of <3% in Belgian children (Lebecque *et al*, 2006). There are, however, important negative effects to be considered before adopting this proactive approach, e.g. the increased risks of bacterial resistance, the risk of emergence of fungal organisms, the potential toxicity of treatment and the impact on daily life of long term nebulised antibiotic treatments. We can also prevent chronic *P. aeruginosa* infection in the majority of children with less invasive protocols aimed at eradicating new *P. aeruginosa* infection.

Treatment of non-tuberculous mycobacterial infection

We recommend that specific treatment should be considered for patients who are smear positive, and for those with persistent positive cultures and symptoms despite routine antibiotic treatment.

Nebulised amikacin is part of the complex and long term antibiotic regimens for the treatment of the "rapid growers" e.g. *M. abscessus* (Cullen *et al*, 2000). There is no evidence base for dosage but

500mg bd is recommended. This may need reducing to 250mg bd in younger children. The injectable preparation (250mg/ml) should be used and made up to 4mls with sodium chloride 0.9%.

Nebulised vancomycin for the treatment of MRSA

The role of nebulised vancomycin remains uncertain. There are anecdotal reports of efficacy in eradicating MRSA from the respiratory tract of patients with CF (Maiz *et al*, 1998), but there are concerns regarding the possible impact of widespread and longer term use on the emergence of resistance.

Key points

- Regular nebulised antibiotics preserve respiratory function
- Long term treatment is safe
- There is no evidence for the superiority of either TOBI® or colistin
- Patients with chronic *P. aeruginosa* infection should be considered for regular nebulised anti-pseudomonal antibiotic treatment
- Initial treatment should be with nebulised colistin
- If colistin is not tolerated or if clinical progress is unsatisfactory, TOBI® should be used

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