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Nebulised gentamicin—suitable for childhood bronchiectasis

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Abstract

Nebulised antibiotic therapy is an established, safe and effective therapy for cystic fibrosis with chronic pseudomonas infection resulting in improved pulmonary function and reduced hospitalisation. Despite similar respiratory disease, this therapy has not been evaluated in children with non cystic fibrosis bronchiectasis. This study evaluates the suitability of a gentamicin solution and nebuliser combination for use in this population.

Materials and methods: Four millilitres of gentamicin (80 mg) in saline delivered by a PARI LC plus® nebuliser and PARI Turboboy N® compressor was used. The pH, osmolarity, chloride concentration and aerosol particle size was determined. Ten children with non cystic fibrosis bronchiectasis received nebulised antibiotic and had peak gentamicin concentrations measured in sputum and serum. Pulmonary function was measured pre and post nebulisation.

Results: The solution had an osmolarity of 199 mOsm/l, pH of 4.1, chloride concentration of 75 mmol/l and the aerosol a mass median aerodynamic diameter of 3.3 μm. Nebulisation was well tolerated, with no significant change in FEV1. Peak serum levels were at the threshold of detectability (0.3 mg/l). Sputum concentrations had a mean of 624 mg/g and lower 95th confidence interval 25 times the minimum inhibitory concentration for the predominant infecting organism, Haemophilus influenzae.

Conclusion: Nebulisation of 80 mg of gentamicin in saline achieved bactericidal concentrations in sputum, was well tolerated and had negligible systemic absorption making it a suitable choice for this population.

Keywords: Nebulised; Antibiotics; Gentamicin; Paediatric; Bronchiectasis

1. Introduction

The demonstration that long term nebulised antibiotic therapy (NAT) improves lung function and reduces hospitalisation in individuals with cystic fibrosis (CF) with chronic Pseudomonas infection makes it an at-

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tractive therapy to consider for other chronic infective airway diseases (Ramsey et al., 1999). Non CF bronchiectasis (BE) is a cause of significant morbidity and mortality in certain populations. The abnormal irreversible dilatation of bronchial airways is the outcome of various lung insults, often in early childhood. Sputum overproduction, impaired muco-ciliary clearance and intense airway inflammation occur. Airway secretions become intermittently or persistently infected, driving a cycle of inflammation and infection with the potential for disease progression. Achieving bactericidal antibiotic levels within airways secretions is a challenge. Sputum inhibits antibiotic action and is poorly penetrated following oral or intravenous administration, requiring high doses increasing the potential for adverse drug reactions (ADR) (Mendelman et al., 1985; Levy et al., 1983; Currie et al., 1990; Labiris et al., 1999; Klastersky et al., 1981). Inhaled therapy offers more direct access to the site of infection and permits the use of high antibiotic doses without significant systemic absorption.

Not all CF therapies have transferred successfully to BE—mucolytics were found potentially detrimental (Crockett et al., 2004). Studies in adults with BE have shown promising though inconclusive results for NAT (Stockley et al., 1985; Labiris et al., 1999; Orriols et al., 1999; Lin et al., 1997; Hill et al., 1986; Barker et al., 2000; de Lima and Bogossian, 1998). Meta-analysis is not possible due to inconsistent methods, different populations and NAT systems used, however, short term improvements in clinical, microbiological and inflammatory outcomes have been reported. As BE often starts in young children and is progressive, interventions need to begin early if adult morbidity and mortality are to be reduced. We set out to evaluate the clinical efficacy of NAT in childhood BE. Differences between the CF and BE populations, and between adults and children make it necessary to first assess the nebuliser system itself. In choosing the system combination, we considered the microbiology of the target population, cost and availability of antibiotic solutions, and our centre's previous experience with NAT. A gentamicin solution delivered by PARI LC plus® jet nebulizer and PARI Turboboy N® compressor was chosen. Gentamicin has good performance against gram negative organisms, dose dependent pharmacodynamics, a track record for inhalation and is inexpensive. The PARI LC plus® nebuliser was used in pivotal CF trials (Ramsey et al., 1999).

The aim of this study was to evaluate the suitability of this system for childhood bronchiectasis and we set out to examine both the physical properties of the system and the in vitro penetration and absorption of the antibiotic. Serum gentamicin levels are a determinant of systemic aminoglycoside toxicity; solution pH, osmolarity and anion content determine tolerability for inhalation; and the mass median aerodynamic diameter (MMAD) of the nebulised output determines the level of airway penetration. Describing these parameters also allows comparison with other systems. Sputum gentamicin level, a surrogate marker for microbiological efficacy, was the primary outcome of the study and used to indicate whether the dose and delivery were theoretically adequate.

2. Materials and methods

2.1. Subjects

Children aged 5–15 years with known bronchiectasis were recruited as they presented to an urban tertiary children's hospital. Inclusion criteria were bronchiectasis diagnosed on high resolution computer tomography, the ability to perform pulmonary function tests and expectorate sputum. Exclusion criteria included cystic fibrosis, renal impairment, pregnancy, recent gentamicin use or gentamicin hypersensitivity. Participants on inhaled steroids were included but were asked not to use short or long acting bronchodilators within 12 h of nebulisation. Participants were evaluated medically on the day of the trial.

2.2. Medication

The 2 ml of 40 mg/ml gentamicin sulphate (Pharmacia NZ Ltd., 602 Great South Rd, Ellerslie, Auckland, New Zealand) was diluted with 2 ml of 0.9% saline (Astra Pharmaceuticals NZ Ltd., 303 Manukau Rd, Epsom, Auckland, New Zealand). The solution was analysed five times using a calibrated Westcore 552 Vapour Pressure Osmometer and Schott CG840 pH meter. Chloride concentration and gentamicin con-

tent were calculated from the manufacturers package inserts. The solution contained disodium edetate.

2.3. Nebuliser and compressor system

A PARI LC plus® nebuliser driven by PARI Turboboy N® compressor (PARI GmbH, Moosstrasse 9, D-82319 Starnberg, Germany) was used. The airflow output of the compressor was measured using a thermal mass flowmeter (model 4140, TSI Incorporated, MN, USA) connected directly to the outflow port and in series with a nebuliser bowl filled with 4 ml of the study solution. Airflow was measured every minute for 10 min. The aerosol output was measured by laser diffraction (Mastersizer S, Malvern Instruments, Malvern, UK) according to methodology described by Clark (1995). Measurements were made at 1 and 4 min on six separate 'runs'.

2.4. Pulmonary function testing

Pulmonary function was measured before and 20 min after nebulisation using a portable electronic spirometer (Vitalograph Compact II, Vitalograph Ltd., Maids Moreton, Buckingham, MK18 1SW, UK) according to American Thoracic Society criteria and calibrated daily. Percentage predicted was calculated using Polgar and Promadhat (1971).

2.5. Nebulisation

The participants were asked to breath normally through the nebuliser. The nebuliser was tapped periodically to improve efficiency. Nebulisation was defined as complete when the bowl appeared empty and no further aerosol came from the mouthpiece. Participants were observed for cough and distress during nebulisation, for 60 min afterwards and were asked if they experienced any change in their ease of breathing.

2.6. Sputum analysis

Participants washed out their mouths with water after nebulisation and provided a sputum sample after 10 min (estimated peak) (Ramsey et al., 1999). Samples were sent immediately to the hospital laboratory and stored at −20 °C until assay. Gentamicin concentrations were measured using commercial fluorescence polarisation immunoassay (Abbott Laboratories, Abbott Park, IL, USA) on an Abbott A×SYM analyser and methodology modified from Labiris et al. (1999). Methods were validated using spiked control sputum samples and results are expressed per gram of sputum, corrected for dilution.

2.7. Serum analysis

A blood sample was obtained 60 min (estimated peak) after the end of nebulisation (Ramsey et al., 1999). Serum was assayed for gentamicin by a commercial fluorescence polarisation immunoassay (Abbott Laboratories, Abbott Park, IL, USA) on an Abbott A×SYM analyser.

2.8. Consent and ethics

The study had approval from the Auckland Ethics Committee, the Maori Research Review Committee and hospital management and written informed consent was obtained from participants and their guardians.

2.9. Data analysis

Compressor flow rates, mass median aerodynamic diameter and solution properties are expressed as means with standard deviation. Change in FEV1 was calculated subtracting FEV1 pre (litres) from FEV1 post (litres) and dividing FEV1 pre (litres). Ninty-five percent confidence intervals (CI) are provided.

3. Results

3.1. Nebulizer system

The 4 ml gentamicin solution had a pH of 4.13 (CI 4.06–4.20), osmolarity of 199 (95% CI 198–200), chloride and gentamicin concentrations of 75 mmol/l and 20 mg/ml, respectively. During nebulisation the compressor had a mean output of 7.2 l/min (95% CI 7.16–7.23). The aerosol had a mean mass median aerodynamic diameter of 3.3 μm (geometric standard deviation 2.1 μm).

Table 1
Characteristics of source population and study participants

	Source population (5–15 years; $n = 56$)	Participants ($n = 10$)
Age: years, mean (range)	12.0 (5–15)	12.1 (8–15)
Female (%)	49	60
Regular inhaled corticosteroid use (%)	38	50
Bronchiectasis (% bilateral, median lobes)	87; 4 lobes	100, 4 lobes
Sputum cultures results in last year		
Haemophilus influenzae (%)	64	100
Staphylococcus aureaus (%)	5	0
Pseudomonas aeruginosa (%)	4	0
Ascribed aetiology of bronchiectasis		
Unknown (%)	44	40
Post infectious (%)	33	30
Primary immunodeficiency (%)	6	30
FVC: mean (95% CI)	72.5 (68–77)	71.6 (61–83)
FEV1: mean (95% CI)	60.6 (55–66)	53.4 (42–65)
FEF 25–75: mean (95% CI)	49.0 (41–57)	35.7 (20–52)

3.2. Participant demography and clinical details

Over 100 children with non CF bronchiectasis were known to the enrolling hospital, 56 aged 5–15 years. Eleven families were approached in April and May 2003 as they presented. One family declined without giving a reason. Those participating had a mean age of 12.1 years, were 60% female, and had extensive bronchiectasis due to previous infection (30%), immunodeficiency (30%) or unknown cause (40%) (Table 1).

3.3. Spirometry, sputum and serum results

Participants had a mean baseline forced expiratory volume in 1 s (FEV1) of 53% predicted. No significant change in FEV1 was observed after nebulisation with a mean rise of 0.7% (CI −2.8 to 4.2%) relative to the baseline. Mean gentamicin concentration in sputum was 697 mg/g (CI 402–981 mg/g) and serum 0.4 mg/l (CI 0.2–0.5 mg/l) (Table 2). Two families declined venesection. No participant reported discomfort during or after nebulisation, one

Table 2
Spirometry, sputum and serum gentamicin results

Participant no.	Baseline FEV1 (Polgar %)	ΔFEV1 (%)	Sputum concentration (10 min, mg/g)	Serum concentration (60 min, mg/l)
1	34	−6.3	1152	0.2[b]
2	83	+2.9	550	0.4
3	51	+3.9	392	0.5
4	38	+8.5	699	0.2[b]
5	42	0.0	748	0.7
6	45	−7.7	445	0.3
7	75	−3.6	81	0.3
8	61	+6.9	1694	0.2[b]
9	71	+1.6	248	Declined
10	34	+27.0[a]	955	Declined
Mean (95% CI)	53 % (42–65)	+0.7 (−2.8 to +4.2)	697 (402–981)	0.4 (0.2–0.5)

[a] Participant took salbutamol following initial spirometry and prior to nebulising gentamicin. Her result was not used in calculating the mean and confidence intervals.

[b] Gentamicin was undetectable (<0.3 mg/l) in three samples. For the purposes of calculating a mean, median and standard deviation they were assigned a value of 0.2 mg/l (being the maximum undetectable level).

coughed briefly three times but completed the nebulisation.

4. Discussion

The pharmacological goals of NAT are to deliver a bactericidal dose of antibiotic to the affected airways while being simple and quick to administer, highly tolerable and with minimal adverse effects. Our study shows that a 4 ml, 80 mg, solution of gentamicin in saline delivered by a PARI LC plus® nebuliser exceeded target sputum concentrations, was well tolerated and resulted in minimal systemic absorption. Significant bronchoconstriction was not seen. Nebulisers have traditionally been slow, inefficient and may result in both systemic and local adverse effects. Differences between study populations in respiratory dynamics, disease distribution, airway hypersensitivity, systemic pharmacokinetics and microbiology, and between nebuliser systems in dose, solution characteristics and aerosol output will effect deposition and safety. We believe this makes it necessary to evaluate a system in the target population. In sputum, concentrations 10–25 times the minimum inhibitory concentration determined from serum are needed due to antibiotic binding, inhibition and inactivation (Levy et al., 1983; Labiris et al., 1999). Systemic antibiotics do not achieve these high concentrations due to poor sputum penetration and the risk of systemic ADR (Labiris et al., 1999; Currie et al., 1990). NAT delivers high antibiotic concentrations to the airways without significant systemic absorption.

Haemophilus influenzae is by far the predominant organism identified during exacerbations and in chronic infection in our population (Edwards et al., 2003). Gentamicin is an inexpensive and readily available aminoglycoside antibiotic with activity against H. influenzae and a long record of use in NAT in the CF arena. Aminoglycoside activity is dependent on the peak concentration achieved and has significant post dose effects making it ideal for nebuliser therapy (Vogelman and Craig, 1986). In our study the mean gentamicin concentration in sputum (697 mg/g) was over 70 times the maximum MIC for H. influenzae and 95% of children receiving this therapy could expect sputum levels greater than 25 times the highest MIC. These results should be qualified by saying that expectorated sputum at 10 min likely reflects relatively central deposition of nebulised antibiotic, particularly in a population where muco-ciliary clearance may be impaired. However, they compare very favourably with the pivotal trials of Tobramycin Solution for Inhalation (TSI, Chiron Corporation, USA) in CF (Ramsey et al., 1999) and those with TSI or gentamicin in adult BE (Labiris et al., 1999; Barker et al., 2000). TSI is specifically formulated for inhalation, has evidence of safety and efficacy in CF with pseudomonas aeruginosa based on large clinical trials and is the only antibiotic approved for inhaled use (CF). However, the authors were reluctant to evaluate a product in our community that will not subsequently be readily available to them due to cost. We recognise the choice of gentamicin was pragmatic and that the additional cost of TSI may be justified.

Aerosol particle size is a significant determinant of lung deposition. Particles with mass median aerodynamic diameters (MMADs) of between 2 and 5 μm are optimal for deposition in peripheral airways. Smaller particles may be advantageous if there is significant airway obstruction but may also increase unwanted systemic absorption. The MMAD of our nebuliser system was 3.3 μm and 42% of the particles between 2 and 5 μm; 66% between 1 and 5 μm, similar to those quoted by the manufacturer with normal saline (PARI GmbH).

Low grades of reversible toxicity and permanent ototoxicity are the major adverse effects associated with aminoglycoside antibiotics. (Moore et al., 1984a,b) Peak serum levels, a major determinant of systemic toxicity, were at the threshold of detectability and well below recommended safe trough levels for parenteral therapy. Cough and bronchoconstriction are known side effects of inhaled agents. Extremes of acidity, osmolarity (<100 or >1100 mOsm/l) and the absence of a permeant anion have been identified as independent causes (Lowry et al., 1988; Eschenbacher et al., 1984; Elwood et al., 1982; Nikolaizik et al., 1996; Godden et al., 1986). Our solution had an osmolarity of 199 mOsm/l and significant chloride, both similar to TSI which was specifically formulated for inhalation. While gentamicin itself is a weak base, intravenous solutions have pH adjusted to approximately 4 to aid preservation. Our solution had a pH of 4.1 and existing evidence suggest cough and bronchoconstriction do not occur until lower pH readings are reached (Lowry

et al., 1988). The safety and tolerability of additives found in some intravenous preparations has been questioned for inhaled use. The disodium edetate in our solution is found in solutions specifically designed for inhalation and, alone, does not induce bronchospasm in asthma patients. (Asmus et al., 2001) A review of first dose challenges in individuals with cystic fibrosis reported significant (10% fall) bronchoconstriction in 20% of those receiving colomycin, 25% tobramycin (extemporous) and 6.25% gentamicin(Adeboyeku et al., 1998). Significant bronchospasm has been reported in 12% of those receiving TSI (Lamb and Goa, 1999). While not a primary outcome, in our study one third of participants had a fall in FEV1 at 20 min, but none clinically significant (all less than 10%). No child reported discomfort during or after nebulisation and cough was rare and mild.

In conclusions an 80 mg solution of gentamicin delivered by a PARI LC plus nebuliser and Turboboy N compressor achieved bactericidal levels in expectorated sputum in children with non CF bronchiectasis. It was well tolerated without causing adverse effects and is an appropriate choice for a clinical efficacy trial in this population. This study should not be used to justify more than a need for further investigation of nebulised antibiotics in non CF bronchiectasis.

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