The use of colistin in Cystic Fibrosis

Introduction

Colistin is an antibacterial cationic cyclic polypeptide belonging to the group of antibiotics called the polymyxins. It is produced as a secondary metabolite from the spore-forming *Bacillus polymyxa var colistinus*. It is structurally identical to polymyxin E and closely related to polymyxin B.

History of colistin

Colistin was first discovered by Koyama *et al* in 1949, as a fermentation product of the bacteria, *Bacillus colistinus* (Koyama *et al,* 1950). In 1959, an intravenous formulation (colistimethate sodium) was released commercially but was then temporarily abandoned in the Seventies and early 1980's due to reports of a high incidence of nephrotoxicity (Price & Graham, 1970; Koch-Weser *et al,* 1970) and also the increasing use of gentamicin. However interest in colistin was rekindled following a rise in the prevalence of multiresistant Gram-negative strains and it is now widely used for the treatment and eradication of Pseudomonas infections in people with cystic fibrosis (CF) (Littlewood *et al,* 2000). Early clinical reports of severe toxicity with the use of colistin are likely to have occurred as a result of inappropriate patient selection, higher than recommended doses and inappropriate monitoring (Li *et al,* 2005).

Antibacterial activity

Colistin acts as a cationic detergent and interferes with the structure and function of the outer cytoplasmic membrane of bacteria. Colistin also has the ability to bind and neutralise bacterial endotoxins, released during infective exacerbations (Li *et al,* 2005). Colistin is bactericidal and is active in vitro against a range of Gram negative bacteria and also it is highly active against *Pseudomonas aeruginosa* with reported resistance being below 5% (Catchpole *et al,* 1997; Pitt *et al,* 2003). Colistin also has activity against a number of clinically important organisms such as *Acinetobacter species*, *Citrobacter, Escherichia coli, Enterobacter species*, *Haemophilus influenzae*, *Klebsiella species*, *Salmonella species* and *Shigella species* (Catchpole *et al,* 1997).

Pharmacokinetics of colistin

Colistin is a multicomponent antibiotic with colistin A (polymixin E1) and colistin B (polymyxin E2) being the two major components (Li *et al,* 2005). There are two preparations of colistin available for clinical use namely colistimethate and colistin sulphate; both are less toxic than the colistin base. Colistimethate sodium causes less pain upon injection than the base or sulphate and appears to have a superior therapeutic ratio to the sulphate. Colistin sulphate is used orally and topically while sodium colistin methanesulphate is used by injection and inhalation. Sodium colistin methanesulphate is produced by the reaction of colistin with formaldehyde and sodium bisulphite (Li *et al,* 2005). Following parenteral administration of sodium colistin methanesulphate, the principal route of excretion is via the kidneys (65-75%). Sodium colistin methanesulphate is further hydrolysed to colistin following parenteral administration with a half-life of 82-268 min and 139-385 min respectively (Li *et al,* 2003). Oral absorption of colistin is very poor.

Prevalence of *P. aeruginosa* resistance to colistin

A recent survey of reported susceptibility to six commonly prescribed antibiotics of isolates of *P. aeruginosa* from 417 people with CF from 17 hospitals (Pitt *et al,* 2003). Almost half were resistant to gentamicin compared to ceftazidime (39%), piperacillin (32%), ciprofloxacin (30%), tobramycin (10%). Only 3% of strains were resistant to colistin, while 40% were resistant to two or more compounds with ceftazidime in combination with gentamicin, piperacillin or ciprofloxacin being the most common cross resistance (Schulin, 2002). Most strains of *Burkholderia cepacia complex* remain resistant to colistin.

We have recently reported our 10 year prevalence of colistin resistance among isolates of *P. aeruginosa* in the Leeds Adult CF unit (Clifton *et al*, 2005). The resistance remained relatively unchanged, despite the frequent use of intravenous and nebulised colistin in the routine management of people with cystic fibrosis.
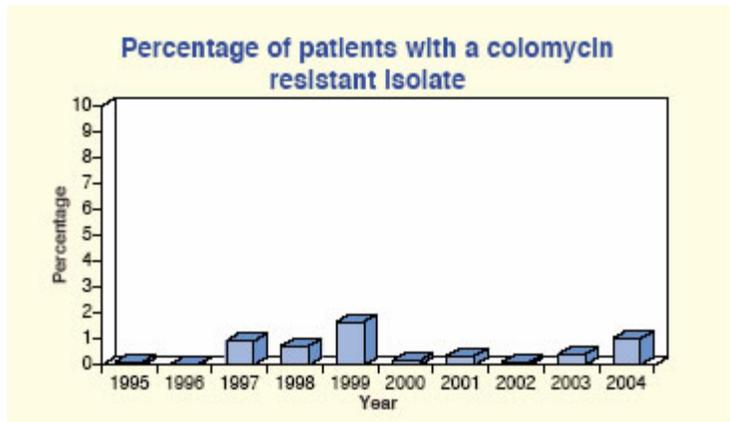

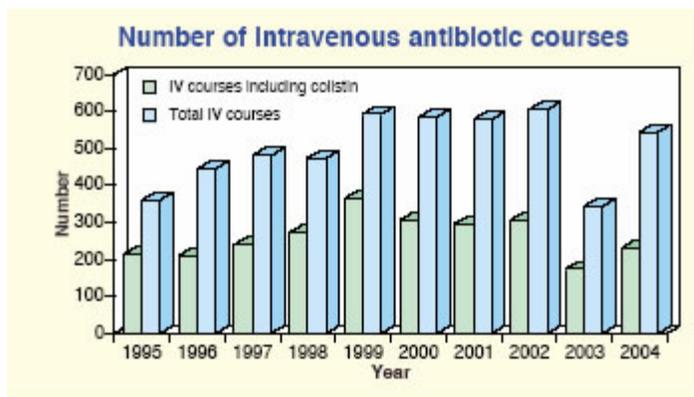Figure 1: Percentage of patients with colistin resistance.

Figure 2: The mean annual number of intravenous antibiotic courses and courses including colistin were 477.7 and 255.6 respectively.
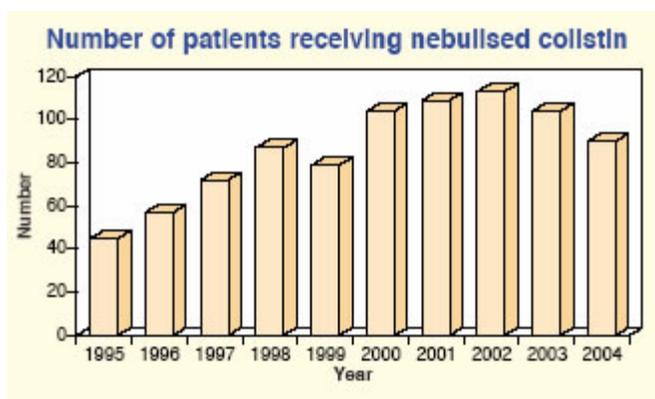

Figure 3: Over the 10 years studied the number of patients receiving nebulised colistin as maintenance treatment increased by 6.2 patients per year.

Long term nebulised colistin for chronic *P. aeruginosa* infection

The regular twice daily administration of a nebulised antibiotic has been an established treatment for chronic *P. aeruginosa* chest infection in CF between exacerbations since Hodson *et al*. published their paper in 1981 comparing nebulised gentamicin and carbenicillin with placebo in a double blind cross-over trial in 20 adult patients (Hodson *et al*, 1981). Subsequent studies have shown improved lung

function, a slower decline in respiratory function, decreased hospital admission rates, better clinical scores, and better weight profile in patients who receive daily nebulised antibiotic treatment. In a meta-analysis of trials using various antibiotics, Mukhopadhyay *et al* concluded that nebulised antibiotics significantly reduced the density of *P. aeruginosa* in the sputum and the frequency of respiratory exacerbations (Mukhopadhyay *et al,* 1996).

So what is the evidence to support the use of nebulised colistin in patients with chronic *P. aeruginosa* infection?

For over a decade, colistin has been used in the UK as routine therapy for patients chronically infected with *P. aeruginosa* (Hoiby *et al,* 2005). Therapy has been found to be safe, and importantly, the emergence of resistant strains does not appear to have become a significant problem.

Two placebo controlled trials looking at the effectiveness of long term nebulised colistin therapy for chronic *P. aeruginosa* infection have been undertaken to date. The first prospective double-blind placebo-controlled study compared nebulised colistin (1 mega unit b.d.) with normal saline (placebo) in 40 patients (age seven to 35 years) over a three month period. Eighteen patients receiving active treatment and 11 in the placebo group completed the study. Colistin was associated with a significantly better clinical symptom score, slower deterioration of pulmonary function (significant for FVC) and reduced inflammatory parameters (Jensen *et al,* 1987).

Day *et al* reported in abstract form, a double blind cross over study comparing colistin (1 mega unit b.d.) with saline in 14 children (age five to 16 years) who were chronically infected with *P. aeruginosa* (Day *et al,* 1988). Following six month treatment, they reported no difference in antibiotic usage although lung function was maintained in the colistin group and declined significantly in patients receiving placebo.

While both studies support the use of nebulised colistin in symptomatic patients with chronic *P. aeruginosa* infection, the study numbers were small. Furthermore, the dose of colistin prescribed could be regarded as suboptimal as most adult CF units in the UK now prescribe 2 mega units b.d. as the standard dose for people over 2 years of age. However, it is unlikely that further studies will be carried out, now that the use of colistin has become part of routine protocol.

Only one study has directly compared tobramycin nebulised solution (TOBI®) and colistin in the clinical setting. Hodson *et al* investigated the efficacy of colistin and tobramycin nebulised solution in 115 people with CF who were chronically infected with *P. aeruginosa* (Hodson *et al,* 2002). Patients were randomised to receive either TOBI (n=53) or colistin (n=62) twice daily for four weeks. Primary end points included the relative change in lung function from baseline. Secondary end points included change in *P. aeruginosa* density, change in MIC and safety. Treatment with TOBI resulted in a significantly greater improvement in FEV_1 (6.7%) when compared to colistin (0.37%), and was associated with a greater improvement in the global rating of change questionnaire with patients showing a relatively greater improvement in their medical condition. Both treatments reduced the bacterial load.

This study had a few weaknesses in its design. Firstly, most patients entered into the study were naïve to TOBI® but many patients had been previously exposed to nebulised colistin prior to the washout period. This exposure was significantly greater than prior exposure to intravenous or nebulised tobramycin in either group. Furthermore the dose of colistin used was only 1 mega unit twice a day which is half the standard dose used by many specialist units in the UK; this may have reduced clinical effectiveness of the drug. Despite the widespread use of colistin over many years, the resistance pattern of *P. aeruginosa* isolates has remained relatively unchanged and long term microbiological surveillance studies for TOBI will need to be carried out to ensure that significant tobramycin resistance does not ensue. Finally, the long term administration of aminoglycosides may also pose a risk of renal toxicity and close monitoring is needed to ensure that treatment does not result in significant nephrotoxicity.

Eradication of early *P. aeruginosa* infection with nebulised colistin

The significance of chronic *P. aeruginosa* infection in CF has lead to developments in strategies to prevent or delay progression from initial acquisition of *P. aeruginosa* to chronic infection. Chronic infection is associated with the mucoid phenotype of *P. aeruginosa*. Whilst acquisition of *P. aeruginosa* may occur quite early in life, the transition from the non-mucoid to the mucoid phenotype may take

several years. Evidence from several studies has shown that early administration of antibiotics, soon after colonization with *P. aeruginosa* has been identified, usually eradicates the organism and significantly reduces the risk of chronic infection (Hoiby *et al*, 2005).

Nebulised colistin has proved highly effective in the early eradication of *P. aeruginosa* infection, resulting in reduced prevalence of chronic infection among children with cystic fibrosis (*Frederiksen et al,* 1997; Lee *et al,* 2004). Littlewood *et al* first reported the effect of inhaled colistin (500,000 units b.d.) on early colonization with *P. aeruginosa* in seven children with CF in 1985. They found that after three to 14 months therapy, there was a significant reduction in the number of positive cultures with three patients having repeatedly negative cultures (Littlewood *et al,* 1985). This was followed by a study conducted by Valerius *et al* where 26 patients elected to receive oral ciprofloxacin plus aerosolized colistin twice daily for three weeks or no treatment in response to an initial isolation of *P. aeruginosa* (Valerius *et al,* 1991). After 27 months of the trial significantly fewer patients who received treatment were positive for *P. aeruginosa* (14% versus 58%, $p < 0.05$). This protocol was further refined by the Copenhagen group to increase the duration of treatment with oral ciprofloxacin and aerosolized colistin to three months. Further follow-up after three-and-a-half years revealed that only 16% of treated patients developed chronic *P. aeruginosa* infection in comparison to 72% of untreated historical controls ($p < 0.005$) (Frederiksen *et al,* 1997).

At the Leeds CF centre we use three months of nebulised colistin in combination with oral ciprofloxacin on first isolation of *P. aeruginosa*. If first line treatment fails we prescribe a further three months of nebulised colistin and two weeks of intravenous (IV) anti-Pseudomonal antibiotics. Alternative nebulised antibiotics such as TOBI are used as part of third line eradication therapy or if colistin is not tolerated. A Leeds audit (unpublished) found no significant difference between the various eradication regimens although there was a trend towards a higher success rate in those individuals who received two weeks IV antibiotics in combination with three months of nebulised colistin.

Intravenous colistin therapy for exacerbations of chest infection

Colistin has proved to be a valuable parenteral antibiotic for the treatment of pulmonary exacerbations in CF. While resistance of *P. aeruginosa* to colistin was unusual; there was an anxiety among health professionals concerning reports of nephrotoxicity and neurotoxicity (Gold and Richardson, 1965; Price *& Graham,* 1970; Koch-Weser *et al,* 1970; Bosso *et al,* 1991). Reported experience of adverse reactions did not include patients with CF and appears to be both reversible and dose dependent. Conway *et al* carried out a randomised study comparing the use of colistin (2 Mega units t.d.s.) versus colistin in combination with a second anti-Pseudomonal antibiotic (Conway *et al,* 1997). A total of 53 patients were entered into the study, 18 of whom were enrolled twice. All patients showed clinical improvement and resolution of their acute exacerbation with no significant difference between the two antibiotic regimens in terms of change in FEV1, FVC, overnight oxygen saturations and clinical scores after 12 days of therapy. The only difference in clinical response was that more patients who received dual therapy had a normal C-reactive protein at the end of treatment. Antibiotic therapy was associated with a statistically significant rise in blood urea and not creatinine at day 12 in both groups. While a significant number of adverse neurological events (dizziness, numbness, tingling, incoordination, unsteadiness, muscle weakness) were reported after direct questioning, only one patient described the symptoms of dizziness and muscle weakness as severe and withdrew from the study. All mild and moderate symptoms were well tolerated and resolved shortly after treatment.

A more recent study by Ledson *et al* reported their four year experience of intravenous colistin in an adult CF unit (Ledson *et al,* 1998). Over the study period, 135 courses (2,414 patient days) of IV colistin (2 Mega units t.d.s.) with an additional anti-Pseudomonal antibiotic were administered to 52 adults with cystic fibrosis. The colistin was safe and effective with treatment being associated with significant improvement in spirometry. There were no adverse effect on renal function and no neurotoxicity. One patient developed a skin rash and another myositis. The addition of colistin to other anti-Pseudomonal drugs also appears to produce greater killing of *P. aeruginosa* than monotherapy (Rynn *et al,* 1999).

Bolus colistin

It is our opinion that colistin as a bolus should not be given to patients without central venous access as in some it may induce significant phlebitis. Colistin can be administered as an intravenous bolus in patients with totally indwelling venous access systems. A small safety study found no serious adverse events (Conway *et al,* 2000); we regularly administer bolus colistin to patients with Port-A-Caths or PAS ports. However patients with peripheral lines experienced mild to moderate injection pain.

Shelf life

Colistin (Colomycin) comes as a sterile powder for solution. It has a shelf life of three years and once in solutions it remains stable for 28 days at 4 oC. Following reconstitution with sterile water, the solution should be used within seven days (*Li et al, 2001*). Colistin ampoules should be protected from light.

Dose of intravenous colistin

Children – (Up to 60 kg) 50,000 to 75,000 units/kg bodyweight per day in three divided doses. (Maximum 75,000 units/kg, in 24 hours)

Adults -75,000 units/kg/day. Standard dose in adults > 60 kg is 2 MU 3 times daily. (Maximum 6 MU per 24 hrs).

The colistin should be diluted with 50 ml 0.9% saline and infused over 30 minutes. If mild neurological side-effects occur, a lower dose of 75,000 units/kg/day in three divided doses should be considered instead of 2 Mega units three times a day.

Colistin may be given as a bolus through a central venous access device with two Mega units being diluted in 10 ml NaCl 0.9% and given over three to five minutes (*Conway et al, 2000*). Bolus colistin should not be given through peripheral lines.

Nebulised dose

Children less than two years - one Mega unit colistin twice daily.

Children over two years of age and standard adult dose - two Mega unit colistin twice daily.

Which nebuliser

The Ventstream and Pari LC Plus, which are used for antibiotics, direct the patient's inspiratory flow through the nebuliser chamber, thereby increasing the effective inhaled nebuliser output. For this to occur the patient's respiratory flow must exceed the compressor flow rate through the nebuliser for a significant proportion of the inspiratory period. This does not always occur in very young children and patients with poor lung function. A mouthpiece rather than a facemask should be used to maximise pulmonary deposition. Relaxed tidal volume breathing through the mouth and not the nose is recommended.

Other devices are available which have perforated oscillating membranes that create the mist for inhalation. This technology creates a more uniform particle size within the respirable therapeutic range. There are currently two devices available - a continuous delivery device called E-flo rapid® (Pari Medical Ltd) and the I-neb® (Respironics / Philips). The I-neb® is an Adaptive Aerosol Device (AAD) which continuously monitors the user's breathing pattern, and only delivers the drug during the first part of inspiration - that being the only part of the inhaled medication which is retained within the lung with continuous delivery devices. This has the added benefit of further reducing treatment time, and does not require venting or filtering of exhaust gases. At present, the I-neb® is only available to those patients on Promixin® (colistimethate sodium) powder for nebulisation (Profile Pharma) which remains more expensive than colomycin.

Assessment of nebulised antibiotics

A formal challenge with pre and post inhalation lung function should be undertaken before instituting therapy.
All patients should be assessed for compliance with therapy and reviewed on a regular basis. It is recommended that patients use nebulised antibiotics after physiotherapy and bronchodilators to ensure maximum deposition and protection from bronchoconstriction.

Adverse effects and contraindications

Colistin and renal disease

Dosage must be decreased in patients with renal dysfunction. Avoid using with aminoglycosides and other nephrotoxic drugs such as non-steroidal anti-inflammatory drugs.

<u>Colistin and liver disease</u>

Although hepatic disease is unlikely to alter the elimination of colistin, no information is available.

<u>Breast feeding</u>

5% of serum level ends up in breast milk. Colistin crosses the placental barrier.

Bronchial constriction

Airway reactivity occurs following the administration of all nebulised antibiotics and in some patients this may lead to the discontinuation of therapy. Bronchoconstriction with a transient fall of FEV_1 after nebulisation has been reported to occur in up to 17.7% of patients (*Dodd et al, 1997; Cunningham et al 2001; Hodson et al, 2002; Alothman et al, 2005*). It is therefore vital that a formal challenge with pre and post inhalation lung function should be undertaken before instituting therapy. Bronchoconstriction can be prevented or lessened by the addition of a beta-2 agonist either before or during nebulisation. A degree of drug tolerance appears to develop over time.

Tonicity of colistin solution

Dodd *et al* conducted a study examining the relationship of chest tightness and change in lung function in response to the inhalation of a range of tonicities of nebulised colistin and their influence on patients' preference (*Dodd et al, 1997*). Twenty seven adult patients with cystic fibrosis inhaled a hypertonic, isotonic, and hypotonic nebulised solution over three consecutive days in random order in a double blind fashion. Measurements of chest tightness, using a visual analogue scale (VAS), and FEV_1 were recorded before and 0, 15, 30, 60, and 90 minutes following inhalation. They found no differences between hypertonic, isotonic, and hypotonic solutions in terms of fall in FEV_1 % predicted and increase in chest tightness. However, the mean time to the maximum fall in FEV_1 % predicted was significantly different between the solutions (hypertonic 7.8 (2.1) min, isotonic 19.2 (5.5) min, and hypotonic 34.2 (5.9) min). There was no correlation between the objective and subjective measurements for any solution.
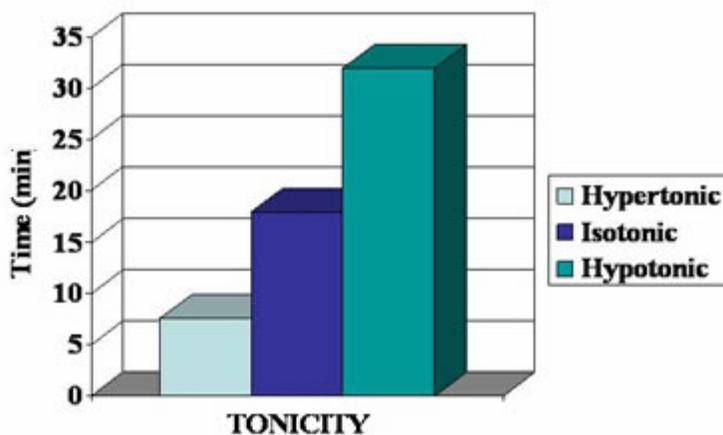
Mean time to maximum fall in FEV_1

Other adverse reactions to colistin - general
- Dizziness
- Confusion
- Visual disturbance
- Numbness, facial paraesthesia
- Vertigo

- Vasomotor instability
- Slurred speech
- Psychosis
- Hypersensitivity
- Local irritation
- Apnoea

Some important contraindications

- Hypersensitivity
- Myasthenia gravis (Gold & Richardson, 1965)
- Pregnancy

Important drug interactions

- Alendronate, etidronate- increased risk of hypocalcaemia
- Aminoglycosides - increases risk of nephrotoxicity, reduce doses if concurrent use essential
- Amphotericin -increased risk of nephrotoxicity
- Loop diuretics - increased risk of ototoxicity
- Muscle relaxants - enhance muscle relaxant effect

Dry powder colistin

Studies on a new dry powder formulation of colistin are in progress and the provisional results are encouraging (Le Brun *et al,* 2002; de Boer *et al,* 2002; Westerman *et al,* 2005). Such therapy appears suitable and highly efficient alternative to nebulisation of antibiotic drugs in CF (de Boer *et al,* 2002). If proven effective, their introduction will result in improvement in patient's compliance and quality of life.

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