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Four years' experience of intravenous colomycin in an adult cystic fibrosis unit

M.J. Ledson, M.J. Gallagher, C. Cowperthwaite, R.P. Convery, M.J. Walshaw

Four years' experience of intravenous colomycin in an adult cystic fibrosis unit. M.J. Ledson, M.J. Gallagher, C. Cowperthwaite, R.P. Convery, M.J. Walshaw. ©ERS Journals Ltd 1998.
ABSTRACT: Nearly all strains of *Pseudomonas aeruginosa* are sensitive to colomycin sulphomethate, but studies in the 1970s using large doses demonstrated significant renal and neurotoxic side-effects and it is not now commonly used. In this study colomycin (2 megaunits *i.v. t.d.s.*) has been used extensively in adult cystic fibrosis (CF) patients and its use reviewed to determine its efficacy and safety profile.

Fifty-two CF patients (28 male, 24 female; mean age 26 yrs, range 17–39 yrs) received 135 courses (mean two courses each, range 1–7, median length 14 days) of *i.v.* colomycin (2,414 patient days in total). It was used in combination with one other *i.v.* antibiotic in 114 courses (85%) and with two others in 18 (13%).

In all cases there was significant improvement in spirometry (pretreatment forced expiratory volume in one second (FEV1) % predicted mean 44.4, range 10–101; post-treatment mean 51.3, range 14–108; p<0.0001). No patient had any neurotoxicity but one developed a skin rash and myositis. There was no change in renal function (urea mean pretreatment 4.1 mmol·L^{-1} (SD 1.4), mean post-treatment 4.3 (2.2), p=NS; creatinine mean pretreatment 77.9 mmol·L^{-1} (15.3), mean post-treatment 80.3 (21.6), p=NS).

In the authors' experience intravenous colomycin sulphomethate in moderate doses is an effective and safe antipseudomonal antibiotic which is easy to administer. Other clinicians should consider its use in patients with cystic fibrosis.
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Regional Adult Cystic Fibrosis Unit, The Cardiothoracic Centre, Liverpool, UK.

Correspondence: M.J. Walshaw
Regional Adult Cystic Fibrosis Unit
The Cardiothoracic Centre
Liverpool L14 3PE
UK
Fax: 44 151 2208573

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Most adult patients with cystic fibrosis (CF) are colonized with *Pseudomonas aeruginosa* [1] and usually require *i.v.* antibiotic therapy to treat pulmonary exacerbations with this organism. Strains of *P. aeruginosa* are showing increasing resistance to conventional antipseudomonal antibiotics [2, 3], yet despite this 98.8% are still sensitive to colomycin sulphomethate, an antibiotic which is easy to administer intravenously. Colomycin is a cationic cyclic polypeptide (sometimes known as polymixin E) isolated from the soil organism *Bacillus colistinus* [4]. The *i.v.* preparation is colomycin sulphomethate, formulated by treating the colistin base with sodium bisulphite in the presence of a formaldehyde [5]. It is bactericidal to many Gram-negative pathogens and works by disrupting the protein and phospholipid layers of the bacterial cell wall [6, 7], causing it to become porous with subsequent cell death [8]. This predominantly physiochemical action may account for the low levels of bacterial resistance seen to this antibiotic [9, 10]. Following parenteral administration, it penetrates most tissues but does not readily cross the blood-brain barrier. Excretion is mainly renal (65–75%) [11].

Despite the apparent suitability of this antibiotic as an antipseudomonal agent, *i.v.* colomycin sulphomethate is not now commonly used, since studies in the 1970s using large doses (up to 26 megaunits (MU)·day^{-1}) demonstrated significant renal and neurotoxic side-effects [12, 13]. Thus, there have been few recent studies reviewing the use of this antibiotic.

Often in combination with other antibiotics, *i.v.* colomycin sulphomethate has been used in more moderate doses to treat pseudomonal chest disease in our adult CF patients for the last 4 yrs. The efficacy and side-effects of this therapy have been reviewed in these patients over this period.

Patients and methods

Fifty-nine CF patients attending the Liverpool adult centre (72% of the clinic) are colonized by *P. aeruginosa*, and 52 of these (88%) have received *i.v.* antibiotics (28 male, 24 female; mean age 26 yrs, range 17–39 yrs, body mass index (BMI) mean 21.8, range 16.4–26.7) for pulmonary exacerbations with the organism. The notes of all 52 patients were reviewed and the number and length of *i.v.* colomycin courses, dose prescribed, other *i.v.* antibiotics concurrently used, use of nebulized colomycin, organisms cultured from sputum and their sensitivities, pre- and post-*i.v.* treatment spirometry and pre- and post-*i.v.* treatment renal function and any side-effects were noted.

Results

Over the study period 135 courses of *i.v.* colomycin at a dose of 2 MU *t.d.s.* were administered to these 52 adult CF patients. Every patient had received at least one course of *i.v.* colomycin (mean two courses each, range 1–7, median length 14 days, longest continuous course 210 days in a severely ill patient). In total, 2,414 patient days of *i.v.*

Table 1. – Sensitivity patterns of the three most common organisms cultured from sputum compared with percentage use of *i.v.* antibiotics used during the study

i.v. antibiotics (dose)		% of courses	% sensitivity of organisms								
			Pseudomonas aeruginosa			*Burkholderia cepacia*			*Staphylococcus aureus*		
			S	D	R	S	D	R	S	D	R
Colomycin	(2 MU *t.d.s.*)	100	100	0	0	0	0	100	0	0	100
Ceftazidime	(3 g *t.d.s.*)	69	70	4	26	0	88	12	95	5	0
Cotrimoxazole	(1.44 g *b.d.*)	16.3	0	0	100	0	75	25	100	0	0
Piperacillin	(4 g *t.d.s.*)	5	69	6	25	0	4	96	20	4	76
Meropenem	(1 g *t.d.s.*)	3.7	74	0	26	-	-	-	100	0	0
Tobramycin	(100–160 mg *t.d.s.*)	3.7	84	2	14	0	0	100	100	0	0
Ciprofloxacin	(400 mg *b.d.*)	1.5	47	5	48	0	0	100	48	0	52
Aztreonam	(2 g *t.d.s.*)	1.5	66	4	30	0	0	100	0	0	100
Imipenem	(500 mg *t.d.s.*)	0.7	65	2	33	0	0	100	95	0	5

Susceptibility tests to all antibiotics were performed using the Stokes disc diffusion method on Diagnostic Sensitivity Testing agar. *Pseudomonas aeruginosa* NCTC 10662 was used as control. Isolates were categorized as: S: susceptible; D: intermediate; or R: resistant, according to the criteria laid down by the National Committee for Clinical Laboratory Standards in 1987. Antibiotic discs were obtained from Oxoid (Basingstoke, UK).

colomycin were given, in combination with one other *i.v.* antibiotic in 114 courses (85%), and with two others in 18 courses (13%) (table 1). Twenty-seven patients (52%) were taking regular prophylactic nebulized colomycin, which was stopped during the acute exacerbation. Improvement was noted in all cases following treatment, and there was a significant improvement in spirometry (pretreatment forced expiratory volume in one second (FEV_1) % predicted mean 44.4, range 10–101; post-treatment mean 51.3, range 14–108; $p<0.0001$).

Sputum pathogens

Two hundred and sixty-eight organisms were cultured from sputum during the 135 courses: 164 (61%) *P. aeruginosa*, 74 (28%) *Burkholderia cepacia*, 14 (5%) *Staphylococcus aureus*, 6 (2%) *Streptococcus pneumoniae*, 5 (2%) *Haemophilus influenzae*, 3 (1%) *Stenotrophomonas maltophilia* and 1 (0.3%) *Streptococcus milleri*. All strains of *P. aeruginosa* were fully sensitive to colomycin sulphomethate.

Side-effects

No patient had any significant neurotoxicity following colomycin, but one individual developed a skin rash and myositis which precluded further use of colomycin.

Fifteen patients (29%) had sensitivity reactions to a total of 12 other *i.v.* antipseudomonal antibiotics and in five patients (10%) this was to two or more antibiotics. Seven patients (13%) were allergic to penicillins and six (12%) to third-generation cephalosporins.

Renal function

Pretreatment and post-treatment renal function data available for 122 courses (90.4%) of *i.v.* colomycin showed no significant change in any parameter (urea mean pretreatment 4.1 $mmol \cdot L^{-1}$ (SD 1.4), mean post-treatment 4.3 (2.2), p=nonsignificant (NS); creatinine mean pretreatment 77.9 $mmol \cdot L^{-1}$ (15.3), mean post-treatment 80.3 (21.6), p=NS) (fig. 1).

Discussion

The mean survival of patients with CF has steadily improved, so that CF infants born today can expect to survive into their fifth decade [14]. This improvement may be a reflection of better nutrition and a more aggressive approach towards respiratory pathogens. In practice, this means more frequent *i.v.* antibiotic use and it is not

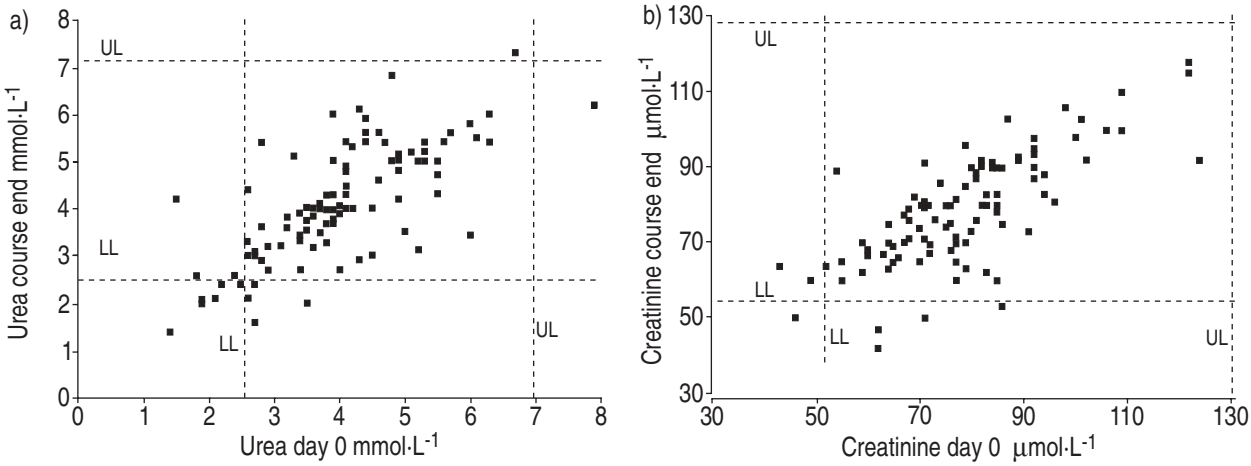

Fig. 1. – a) Urea and b) creatinine levels (paired values). UL: upper limit normal range; LL: lower limit normal range. No significant difference was seen during *i.v.* colomycin administration.

surprising that resistance to antibiotics has therefore increased [2, 3]. However, over the last 4 yrs the *P. aeruginosa* strains in the authors' clinic have remained fully sensitive to colomycin, in contrast to many other antibiotics, possibly as a result of colomycin's physiochemical mode of action [6–10].

Indeed, the efficacy of colomycin against *Pseudomonas* spp. is such that it is the only antipseudomonal antibiotic which is licensed in the UK for use in nebulized form. Despite its excellent sensitivity profile against *P. aeruginosa*, *i.v.* colomycin is not widely used, principally because studies in the 1970s reported high rates of acute renal tubular necrosis and neurological side-effects [12, 13]. However, patients in these studies received massive doses of the drug (up to 26 MU) and many were postoperative, severely ill and septic. Furthermore, they did not suffer from CF; CF patients often require higher doses of *i.v.* antibiotics than normal individuals. In keeping with this, studies looking at antibiotic kinetics in CF patients have shown that they have an increased volume of distribution (corrected for body weight), increased renal excretion [15] and increased biotransformation. All of these factors lower serum levels, such that CF patients may be able to tolerate higher doses of *i.v.* antibiotics without side-effects than non-CF patients. Indeed, in the present study, patients with a low BMI tolerated *i.v.* colomycin without problems. Furthermore, antibiotic penetration in the CF lung is reduced because organisms form microcolonies surrounded by polysaccharides (the biofilm) [17] and, therefore, dosage requirements are increased.

There have been few recent studies reviewing *i.v.* colomycin use [18, 19] and the largest included only 852 patient days [19]. In this much larger study of 2,414 patient days of *i.v.* colomycin, pretreatment and post-treatment renal function showed no significant change and no patient reported any neurological side-effects. However, one patient developed a skin rash and myositis which precluded further use of the drug. This is a better side-effect profile than for many of the other antipseudomonal antibiotics which are used to treat CF patients in our clinic; several patients are allergic to many of the mainline *i.v.* antipseudomonal antibiotics but tolerate colomycin without problems.

The lack of nephrotoxicity and neurotoxicity of this antibiotic in moderate doses has been confirmed by a recent prospective study where *i.v.* colomycin 2 MU *t.d.s.* was given for 12 days as monotherapy to 33 adult CF patients with normal renal function [19]. No significant change in creatinine clearance was noted and proteinuria did not occur. Only mild transient neurological features (numbness, tingling, muscle weakness) were noted and the drug continued to be administered in all but one case.

It is common practice in adult CF clinics to use two or more *i.v.* antipseudomonal antibiotics, to minimize the risk of increasing antibiotic resistance and to encourage synergy. Furthermore, it has been shown that *i.v.* colomycin used as monotherapy results in a far inferior spirometric response to treatment compared with *i.v.* colomycin used as part of a duotherapy regime [19]. In keeping with this, whenever possible *i.v.* colomycin is used in combination with other *i.v.* antibiotics. Using such regimes, in all our patients clinical improvement was observed and a significant improvement in FEV_1 % pred was seen. In addition, *i.v.* colomycin is compatible with many other antibiotics, is easy to prepare and can be administered by patients at home using preprepared drug-delivery devices. This increases patient acceptability and conserves expensive inpatient resources.

In the authors' experience *i.v.* colomycin sulphomethate in moderate doses is an effective and a safe antipseudomonal antibiotic which is easy to administer. Other clinicians should consider its use in patients with cystic fibrosis.

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