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Fosfomycin therapy for multiresistant *Pseudomonas aeruginosa* in cystic fibrosis

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Abstract

Background: Increasing resistance to standard antibiotics has been demonstrated in CF patients colonised by *Pseudomonas aeruginosa.* The antibiotic Fosfomycin has a unique mode of action against this organism, and may protect against aminoglycoside mediated renal and ototoxic effects. However, there is little published experience of this drug in IV form, and it is not licensed for use in the UK. *Methods*: In combination with other antibiotics, we used Fosfomycin to treat 30 pulmonary exacerbations in 15 adult CF patients colonised by *P. aeruginosa,* mainly multiresistant strains. All patients gave informed consent. We cultured sputum prior to treatment and measured spirometry, renal function, and symptoms before and after treatment, and recorded any side effects. *Results*: One patient developed nausea and Fosfomycin treatment was withdrawn. The remaining patients showed clinical resolution of their chest exacerbations (mean FEV1% predicted: pre 41.1 vs. post 49.4, $P<0.001$). Although there was a statistical increase in plasma urea (pre 3.9 mmol/l vs. post 4.3, $P<0.03$), this was still within the normal range. Plasma creatinine was unchanged. *Conclusions*: This study shows that IV Fosfomycin is well tolerated by adult patients with CF and can be useful in the treatment of those colonised with multiresistant *P. aeruginosa*.

Keywords: Novel treatments; Combination antibiotic therapy; Chronic colonisation

1. Introduction

Most adult patients with cystic fibrosis (CF) are colonised with *Pseudomonas aeruginosa*, which in some studies has been shown to confer a poor prognosis [1]. In many of these patients, pulmonary exacerbations require treatment with intravenous combinations of antipseudomonal antibiotics, including aminoglycosides that have been shown to cause auditory [2] and renal [3] toxicity. Furthermore, in cystic fibrosis patients, isolates of *P. aeruginosa* are becoming increasingly resistant to conventional antipseudomonal antibiotics [4] and in our unit of over 140 adult CF patients where 80% are colonised by this organism, 75% are now multiresistant.

We have therefore looked for other antibiotics that possess antipseudomonal activity. One such antibiotic is fosfomycin (1,2-epoxypropylphosphonic acid) originally isolated in 1969 from *Streptomyces fradiae* and other *Streptomyces* species [5] but now produced synthetically.

Fosfomycin is a unique broad-spectrum bactericidal antibiotic [6] chemically unrelated to any other known antimicrobial agent. It is available in oral formulations as fosfomycin calcium or fosfomycin trometamol, and in intravenous formulation as fosfomycin disodium. Following intravenous administration of the disodium salt 80–95% of the drug is excreted unchanged in the urine by glomerular filtration within 24 h, the serum half-life is 1.5–2 h, the antibiotic is not bound to serum proteins and its volume of distribution is large [7,8]. Its diffusion into tissues and body fluids including cerebrospinal fluid is good [9]; the concentration of fosfomycin in lung tissue can be up to 50% of serum levels 1–2 h after administration [10]. It is taken up actively into bacterial cells through two nutrient transport systems present in various bacteria (including *P. aeruginosa*), and inhibits the initial step in cell wall synthesis [11]. However, in vitro susceptibility testing for fosfomycin against *P. aeruginosa* requires the presence of glucose-6-phosphate, which is not routinely incorporated into standard sensitivity testing agars. Thus without this, sensitive strains may appear resistant [12]. Furthermore,

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Table 1
Sensitivity patterns of the three most common organisms found in sputum culture and use of intravenous antibiotics used during the study

IV antibiotics (dose)		% courses	% sensitivity of organisms								
			Pseudomonas aeruginosa			*Burkholderia cepacia*			*Staphylococcus aureus*		
			S	*I*	*R*	*S*	*I*	*R*	*S*	*I*	*R*
Ceftazidime	3 g tds	19	24.6	8.2	67.2	0	100	0	33.3	0	66.7
Colomycin	2 MU tds	32	100	0	0	0	0	100	0	0	100
Tobramycin	140–160 mg tds	32	83.6	4.9	11.5	0	0	100	100	0	0
Meropenem	1 g tds	32	31.1	8.2	60.7	0	0	100	100	0	0
Aztreonam	2 g tds	0	23	8.2	68.8	0	0	100	0	0	100
Cotrimoxazole	1.44 g bd	6	0	0	100	0	100	0	100	0	0
Imipenem	500 mg tds	0	21.3	4.9	73.8	0	0	100	100	0	0
Piperacillin	4 g tds	0	27.9	6.6	65.5	0	0	100	0	0	100
Gentamicin	140–160 mg tds	0	23	9.8	67.2	0	0	100	100	0	0
Ciprofloxacin	400 mg bd	0	42.6	8.2	49.2	0	0	100	0	0	100

Key: S = sensitive; I = intermediate sensitivity; R = resistant.

it has been suggested that fosfomycin may protect against aminoglycoside nephro—[13,14] and oto—toxicity [15,16].

Thus it would seem that fosfomycin might be an effective antibiotic, as part of combination intravenous therapy, for the treatment of pseudomonas pulmonary exacerbations in CF, with the added benefit of conferring renal and auditory protection from concomitant aminoglycoside use. However, we are not aware of any studies that have used this antibiotic in CF patients. We have therefore examined the efficacy and side effects of fosfomycin used as part of combination therapy over a 5-year period in a group of adult CF patients with multiresistant *P. aeruginosa* infections.

2. Patients and methods

Because fosfomycin is not licensed for use in the UK, we have only given it to patients with pulmonary exacerbations where there was pathogen multiresistance or patient intolerance to standard antipseudomonal antibiotics, or if patients had developed dose related side-effects (such as renal and oto-toxicity with aminoglycosides). Fosfomycin was prescribed at a dose of 5 g tds and imported from Germany for these individuals on a named patient basis. Overall, 15 patients [mean age 23 years (range 18–37 years), 9 female] received fosfomycin and they formed the study population.

The number and length of courses of intravenous fosfomycin, the dose prescribed, other intravenous antibiotics co-administered, pre- and post-treatment spirometry, pre- and post-treatment serum urea and creatinine, bacteria cultured from sputum and their sensitivities [17] and any reported side effects were recorded.

2.1. Statistics

Results are expressed as mean plus (S.D.) or (range) as appropriate. Comparisons were made using paired *t*-tests. A P value of <0.05 was considered significant.

3. Results

A total of 30 courses of fosfomycin were prescribed [mean 2 courses per patient, (range 1–3), course length mean 16.6 days (range 7—36)]; in combination with one other intravenous antibiotic in 20 courses (67%) and with two others in 10 courses (33%) (Table 1). Overall, a total of 499 days of fosfomycin therapy were given.

3.1. Spirometry

There was a significant increase in spirometry after fosfomycin combination treatment [FEV_1% predicted: pre-treatment mean 41.1 [range 14–96), post-treatment mean 49.4 (range 16–97); $P<0.001$] (Fig. 1).

3.2. Renal function

Pre- and post-treatment renal function data were available for 24 courses of fosfomycin. There was no change in serum creatinine (pre-treatment: mean 85 umol/l (S.D. 27.6), post-treatment: mean 78.1 μmol/l (S.D. 14.8): (P = NS) (Fig. 2). Whilst there was a statistical increase in urea following treatment (pre treatment: mean 3.9 mmol/l (S.D. 1.7), post-treatment mean: 4.3 mmol/l (S.D. 1.6) ($P<0.03$), this was not clinically significant (Fig. 3).

3.3. Sputum pathogens

All patients were infected with multiresistant *P. aeruginosa* (61 isolates). In addition, 3 patients were co-infected with *Staphylococcus aureus*, 1 with Haemophilus influenzae, 1 with *Proteus* spp., and 3 with *Burkholderia cepacia.* Sensitivity patterns of the three most common organisms found in sputum culture and use of other intravenous antibiotics used during the study are given in Table 1. Sensitivity patterns to

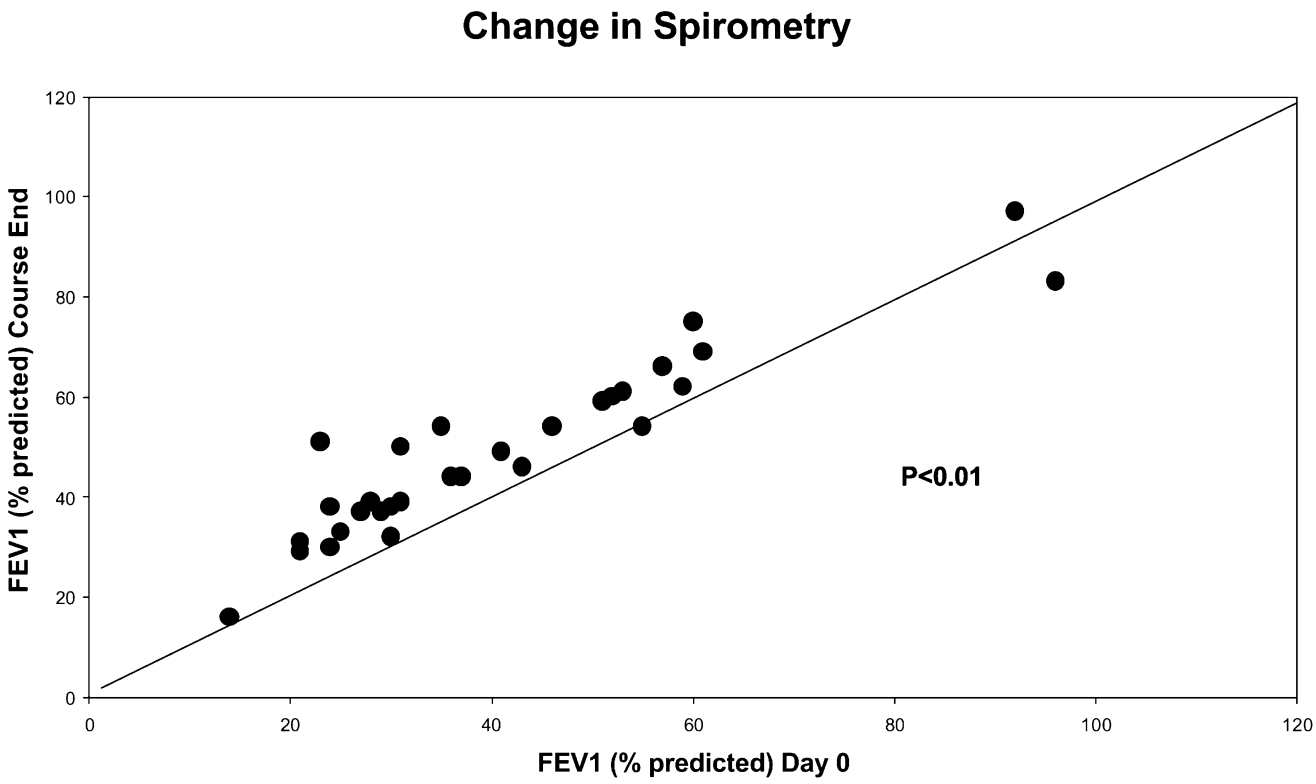

Fig. 1. Change in spirometry with fosfomycin treatment.

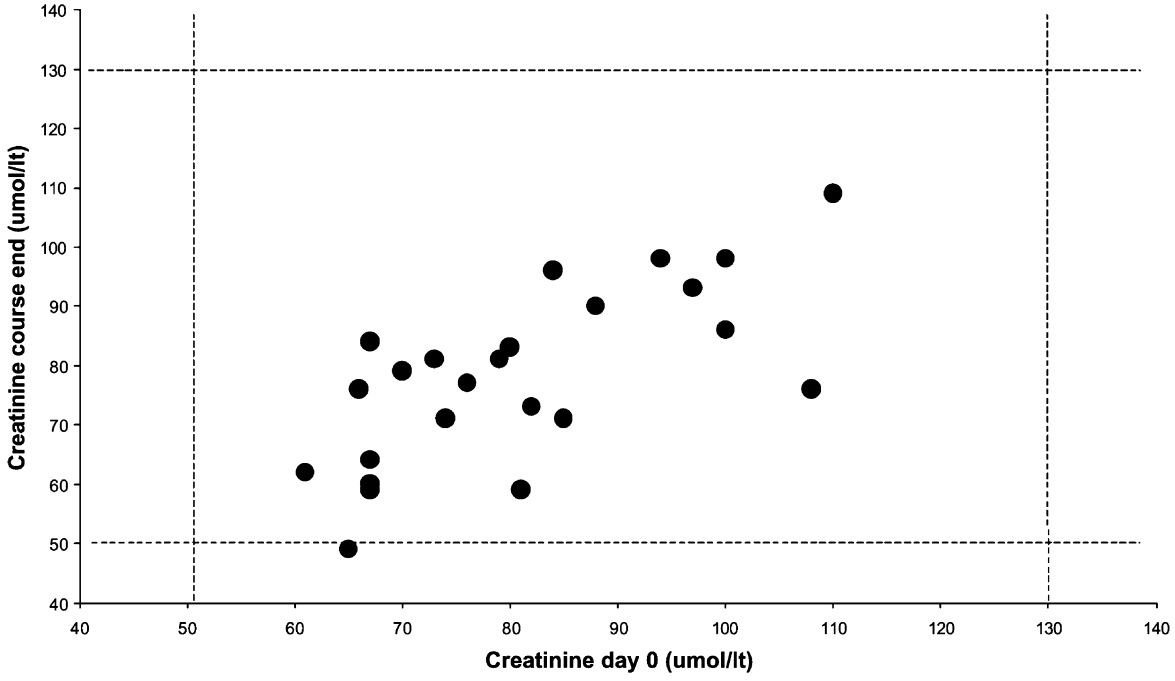

Fig. 2. Change in serum creatinine with fosfomycin treatment. The broken lines indicate the limits of the normal range.

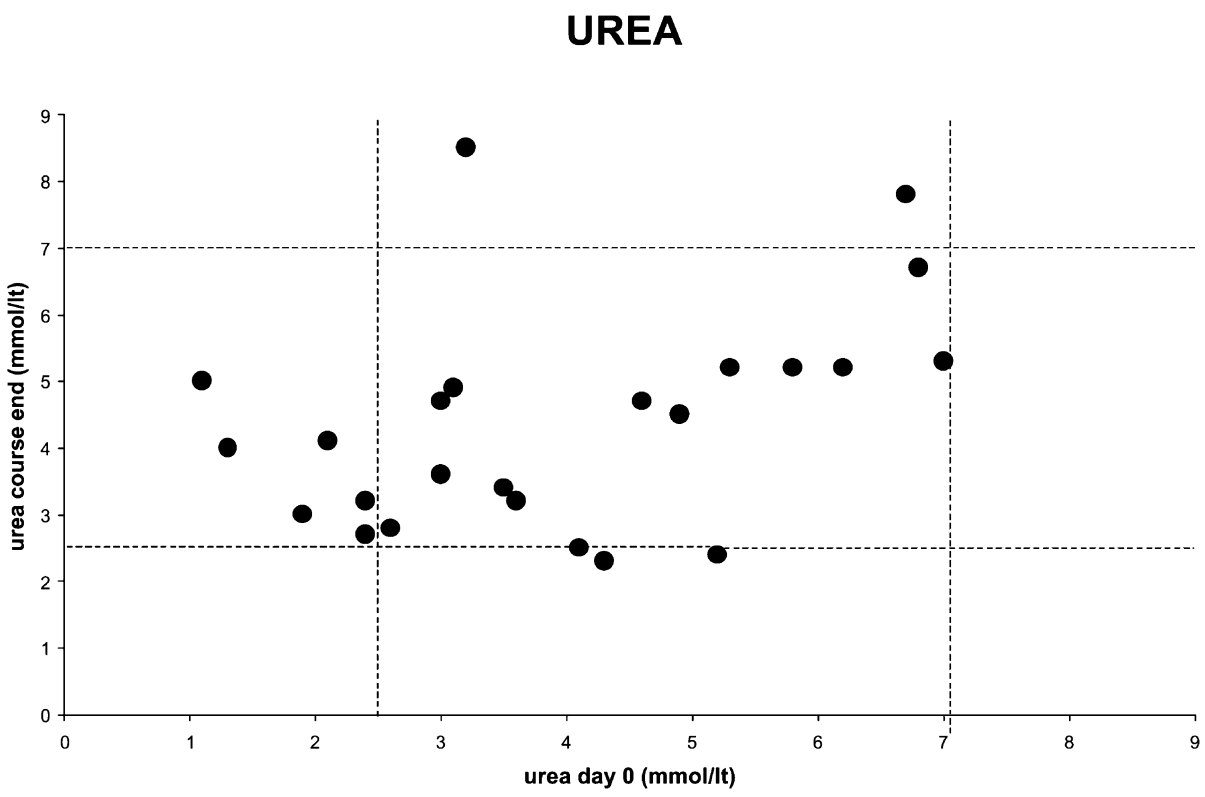

Fig. 3. Change in serum urea with fosfomycin treatment. The broken lines indicate the limits of the normal range.

fosfomycin were not included because of the difficulty in obtaining therapeutically meaningful results, as illustrated earlier. Nevertheless, 8 of the 15 patients (53%) had strains sensitive to fosfomycin using this method.

3.4. Side effects

One patient experienced nausea during combination treatment with fosfomycin, and the drug was withdrawn.

4. Discussion

Patients with cystic fibrosis who are infected with *P. aeruginosa* will require repeated courses of intravenous antipseudomonal antibiotics for pulmonary exacerbations. This repeated use of a limited selection of antibiotics encourages the development of resistance, and many adult patients with CF now harbour multiresistant *P. aeruginosa* strains [4]. Furthermore, repeated use of the same antibiotics results in patient intolerance and increased side effects. Thus, in such patients fosfomycin may be useful when co-administered with other antibiotics for a number of reasons.

Firstly, the vigorous inflammatory response in the CF lung encourages *P. aeruginosa* to form microcolonies surrounded by negatively charged polysaccharides (the biofilm or glycocalyx) [18,19]. This biofilm allows the persistence of the organism in the face of specific antibodies and antibiotics [20]. However, in vitro fosfomycin does not react with the negatively charged glycocalyx and in vivo may therefore be able to penetrate the biofilm [21].

Secondly, in vitro a synergistic effect has been demonstrated in combination with ofloxacin against *P. aeruginosa* growing in a biofilm [22], and with ciprofloxacin against *P. aeruginosa* isolates from CF patients [23]. This may be because fosfomycin acts on different synthetic pathways, demonstrating synergy against *P. aeruginosa* when used in combination with a wide variety of other antibiotics including β-lactams, aminoglycosides, macrolides and tetracyclines [24–29].

Thirdly, because fosfomycin acts on synthetic pathways unaffected by other agents, the potential for the development of cross-resistance with other classes of antibiotics is reduced [30].

Fourthly, when co-administered, fosfomycin has been shown to reduce aminoglycoside-associated nephrotoxicity by protecting lysosomal membrane integrity [13,31]. A similar mechanism may account for protection against aminoglycoside-related ototoxicity [15,16].

Finally, fosfomycin has an excellent side-effect profile. Indeed, the main side effects are gastrointestinal (nausea, vomiting, diarrhoea and a transient increase in serum transaminase levels) thought to be most common

with the oral preparations, occurring in 2–8% of cases [32,33]. Mayama et al. reported pseudomembraneous colitis and melaena in only 2 out of 35481 cases, again with oral formulations of fosfomycin [34]. There are no specific reports in the literature of side effects with the IV preparation.

Despite all these potential advantages of fosfomycin, to the authors' knowledge it has not previously been used in combination with other intravenous antibiotics in the management of pulmonary exacerbations in CF patients in the UK. Our study of 499 patient days of fosfomycin use has demonstrated that significant improvements in spirometry were obtained without compromising renal function and with minimal side effects. Only one patient reported nausea with fosfomycin, which had to be discontinued. Meaningful sensitivity profiles to fosfomycin were not reported in this study, since the media used routinely for in-vitro testing do not include glucose-6-phosphate and sensitive strains may therefore appear resistant [12]. Even using this method, however, over half our patients harboured *Pseudomonas* strains sensitive to fosfomycin. Other workers have found similar patterns [29]. Furthermore, Wolter et al. found no correlation between clinical outcome parameters and susceptibility of *P. aeruginosa* colonies to the antibiotics used in a group of adult CF patients [35].

Thus, in our experience, fosfomycin given intravenously in combination with other antibiotics for pulmonary exacerbations in CF patients colonised by multiresistant *P. aeruginosa* resulted in clinical improvement with a low side effect profile. We recommend its use to other CF centres where multiresistant strains are common.

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