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Intravenous fosfomycin for pulmonary exacerbation of cystic fibrosis: Real life experience of a large adult CF centre

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ABSTRACT

Background: The increased prevalence of multi-drug resistant strains of *P.aeruginosa* and allergic reactions among adult patients with cystic fibrosis (CF) limits the number of antibiotics available to treat pulmonary exacerbations. Fosfomycin, a unique broad spectrum bactericidal antibiotic, might offer an alternative therapeutic option in such cases.

Aim: To describe the clinical efficacy, safety and tolerability of intravenous fosfomycin in combination with a second anti-pseudomonal antibiotic to treat pulmonary exacerbations in adult patients with CF.

Method: A retrospective analysis of data captured prospectively, over a 2-years period, on the Unit electronic medical records for patients who received IV fosfomycin was performed. Baseline characteristics in the 12 months prior treatment, lung function, CRP, renal and liver function and electrolytes at start and end of treatment were retrieved.

Results: 54 patients received 128 courses of IV fosfomycin in combination with a second antibiotic, resulting in improved FEV1 (0.94 L vs 1.24 L, $p < 0.01$) and reduced CRP (65 mg/L vs 19.3 mg/L, $p < 0.01$). Renal function pre- and post-treatment remained stable. 4% (n = 5) of courses were complicated with AKI at mid treatment, which resolved at the end of the course. Electrolyte supplementation was required in 18% of cases for potassium and magnesium and 7% for phosphate. Nausea was the most common side effect (48%), but was well controlled with anti-emetics.

Conclusion: Antibiotic regimens including fosfomycin appear to be clinically effective and safe. Fosfomycin should, therefore, be considered as an add-on therapy in patients who failed to respond to initial treatment and with multiple drug allergies.

1. Introduction

Cystic fibrosis (CF) is a multi-system condition, characterised by chronic endobronchial infection, recurrent pulmonary exacerbations and progressive lung damage. The severity of lung disease, colonisation and infection with *P.aeruginosa* are among the main determinants of morbidity and mortality in patients with CF [1,2]. Early antibiotic therapy and the availability of anti-pseudomonal drugs have significantly improved survival of patients with CF over the past few decades. In recent years, however, an increased prevalence of multi-drug resistant (MDR) strains of *P.aeruginosa* and drug-hypersensitivity reactions has limited the effectiveness and number of antibiotics available for the treatment of acute pulmonary exacerbations [3,4]. This has led to a resurgence in the interest in less conventional and older drugs such as fosfomycin.

Fosfomycin is a unique broad-spectrum antibiotic derived from phosphonic acid, which is active against both Gram-positive and Gram-negative bacteria and anaerobic pathogens. Its bactericidal action is reinforced by a synergistic effect with other antibiotics, such as beta-lactams and aminoglycosides [5]. Fosfomycin inactivates the enzyme pyruvyl-transferase and inhibits the formation of *N*-acteylmuramic acid and thus, the synthesis of peptidoglycan, interfering therefore with the bacterial wall synthesis [6]. It is available as either oral or intravenous formulation, and anecdotally has been used subcutaneously [7].

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Bioavailability, following oral administration, is low and highly variable (12–40%), depending on intra-gastric acidity and gastric emptying rate. This leads to difficulties in achieving a high C_{max}/MIC, therefore oral fosfomycin is not suitable for the treatment of systemic infections including pulmonary exacerbations in CF [8–10]. Conversely, fosfomycin, administered intravenously, has a large distribution volume and good penetration in the lungs [11]. Its half-life is approximately 2 h, and it is excreted largely unchanged by the kidneys [6,12].

By virtue of its pharmacokinetics and pharmacodynamics properties, fosfomycin is being extensively studied as a means to treat Gram-positive and Gram-negative related lower respiratory tract, urinary tract, soft tissue and nosocomial infections in critically ill patients with positive results [13–19]. Over the past two decades, IV fosfomycin has been used in combination therapy to treat MDR-*P.aeruginosa* related pulmonary exacerbation in patients with CF. These data, however, are limited to small retrospective case series [7,20–23].

We report our experience in the use of IV fosfomycin as part of combination antibiotics regimens for pulmonary exacerbations in patients with CF, focusing on its efficacy, safety and tolerability.

2. Methods

2.1. Study design

A retrospective analysis of data captured prospectively on the electronic patients' records [EPRs (EMIS®)] in patients attending the Leeds Regional Adult Cystic Fibrosis Centre was performed. All patients previously consented for their clinical information to be used for research purposes.

2.2. Patients

Patients, aged 17 or older, who received at least one course of IV fosfomycin (4 g four times daily or reduced dose 2 g four times daily) in combination with a second anti-pseudomonal antibiotic for an acute pulmonary exacerbation between July 2014 and July 2016 were included in the study. Patients who received lung transplant were excluded.

In our Unit, criteria for prescribing fosfomycin were: limited antibiotic choice due to multiple drug allergies, or poor response to initial treatment.

2.3. Data collection

The EPRs were searched for all courses of IV fosfomycin, and all patients who met the eligibility criteria were included. Baseline demographics, comorbidities and microbiology status at the first course were recorded, as well as the best lung function and BMI in the 12 months preceding the first course of IV fosfomycin. For each course of treatment which included IV fosfomycin, pre- and post-treatment blood results were retrieved. Lung function at start and end of the course was also recorded. Electronic medical notes were reviewed to record patients' reported side effects.

2.4. Statistical analysis

A paired T-test was performed to compare variables, which were normally distributed, and a Wilcoxon Signed Ranks Test if the distribution was not normal. The Chi-square test was used to assess differences in frequency distributions between groups.

Post-hoc analyses were performed to assess differences in clinical efficacy and tolerance based on the reasons to start fosfomycin treatment and to ascertain any differences in outcome (lung function and CRP) based on *P.aeruginosa* phenotype identified at start of treatment.

All tests were two-sided and significance level was set at $p < 0.05$. Data are reported as mean and SD, if normally distributed, and as median and IQR if not. IBM SPSS statistics version 24 (IBM Corp, Armonk, NY, USA) was used for all the analyses.

Table 1
Patients' characteristics.

Age, yrs	32.3 ± 8.3
Sex, F (%)	31 (57.4%)
Best FEV_1 (L)	1.35 (0.95)
Best FEV_1 (%)	42 (28.5)
Best FVC (L)	2.43 (1.29)
Best FVC (%)	64.5 (23.3)
Best BMI	22.1 (4.69)
LTOT, (%)	17 (31.5%)
NIV, (%)	2 (3.7%)
CFRD, (%)	27 (50%)
Pancreatic insufficiency, (%)	51 (94.4%)
Enteral feeding, (%)	13 (24.1)
Microbiological status	
Pseudomonas aeruginosa	
Chronic	53 (98.1%)
Intermittent	1 (1.9%)
Free	0 (0%)
MSSA, (%)	14 (26%)
MRSA, (%)	3 (5.6%)
Achromobacter xylosoxidans, (%)	4 (7.4%)
Pandoraea sp, (%)	2 (3.8%)
Stenotrophomonas maltophilia, (%)	16 (29.7%)
Burkholderia cepacia complex, (%)	1 (1.9%)
Allergies	
Tobramycin, (%)	21 (38.9%)
Colomycin, (%)	29 (53.7%)
Amikacin, (%)	6 (11.1%)
Meropenem, (%)	30 (55.6%)
Ceftazidime, (%)	33 (61.1%)
Aztreonam, (%)	20 (37%)
Piperacillin/tazobactam, (%)	40 (74.1%)
Ciprofloxacin, (%)	8 (14.8%)

Data are expressed as mean (SD) when normally distributed and as median (IQR) when not normally distributed. Obsereved number of cases and frequency is reported. Best lung function and BMI refers to the best recorded measurement in the 12 months preceding the first antibiotics course including IV fosfomycin. CFRD, cystic fibrosis related diabetes. LTOT, long term oxygen therapy. NIV, noninvasive ventilation.

3. Results

3.1. Patients

Over the study period, 438 patients were under follow-up at the Leeds Regional Adult CF Centre; 54 met the eligibility criteria and received at least one course of IV fosfomycin. Table 1 summarises the baseline characteristics of patients.

3.2. IV courses

A total of 128 courses of IV fosfomycin were prescribed: 23 patients (42.6%) received more than one course. IV fosfomycin was always prescribed as part of a combination regimen with at least a second IV antipseudomonal antibiotic. In 28 courses fosfomycin was prescribed in combination with colomycin and in 16 courses with tobramycin only or in combination with a beta-lactam. In the remaining 84 cases fosfomycin was prescribed in association with beta-lactams (78) or ciprofloxacin (6).

Seventy-one (55.5%) courses of IV fosfomycin were given due to multiple drug allergies, and 57 (45.5%) due to failure of initial treatment. Forty-seven (36.7%) sputum samples were positive for non-mucoid *P.aeruginosa,* 81 (63.3%) for mucoid *P.aeruginosa* or for both phenotypes.

Overall, the median duration of IV antibiotic treatment was 17 (20) days, and of IV fosfomycin was 11 (6) days.