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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 effects (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.

Keywords

Fosfomycin; *P.aeruginosa*; pulmonary exacerbation; cystic fibrosis

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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 and colonisation 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]. 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, making therefore oral fosfomycin not suitable for the treatment of systemic infections including pulmonary exacerbations in CF. Following IV administration, on the other hand, ~~it~~ fosfomycin has a large distribution volume and good penetration in the lungs[8]. Its half-life is approximately 2 hours; and it is excreted largely unchanged by the kidneys [6,9].

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 tissues and nosocomial infections in critically ill patients with positive results[10–16]. 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[7,17–20].

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.

Methods

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.

Patients

Patients, aged 17 or older, who received at least one course of IV fosfomycin (4 g QDS or reduced dose 2 g QDS) 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.

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.

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.

~~A p~~Post-hoc analyses~~is~~ were~~as~~ 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.

Results

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.

Table 1 Patients' characteristics	
Age, yrs	32.3 ± 8.3
Gender, F (%)	31 (57.4%)
Best FEV1 (L)	1.35 (0.95)
Best FEV1 (%)	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 insufficency, (%)	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.

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 ~~in all other~~ 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 strains.

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

Post-hoc analysis based on the reasons for prescribing showed a similar duration of treatment between groups, but total length of a course of IV antibiotic was longer for patients who failed initial treatment than those with multiple drug allergies [29 (22) vs 13 (5), p<0.01].

Lung function

FEV_1 and FVC increased significantly in the whole population and in ~~the~~ each of the~~two~~ cohorts identified based on the reason to start fosfomycin and on the *P.aeruginosa* phenotype (all p<0.01) (Fig 1, Table 2). A significant increase in $FEF_{25-75\%}$ was observed in the groups combined (p<0.01), independently on the strain of *P.aeruginosa* (p<0.05), and in

patients with multiple drug allergies (p<0.05), but not in in the group who failed initial therapy (Table 2).

Table 2 Lung function at start and end treatment

	Start treatment	End treatment	*p*
FEV1 (L)	0.94 (0.76)	1.24 (0.99)	<0.01
Drug allergies	1.11 (0.75)	1.37 (1.03)	<0.01
Failure of initial therapy	0.80 (0.60)	0.92 (0.78)	<0.01
Mucoid P.aeruginosa	0.9 (0.74)	1.18 (0.9)	<0.01
Non-mucoid P.aeruginosa	1.32 (0.92)	1.47 (1.18)	<0.01
FEV1 (%)	32 (22)	37 (26)	<0.01
Drug allergies	35 (19)	41 (31)	<0.01
Failure of initial therapy	23 (14)	27 (17)	<0.01
Mucoid P.aeruginosa	27 (20)	39 (24)	<0.01
Non-mucoid P.aeruginosa	32 (24)	37 (38)	<0.01
FVC (L)	1.69 (1.18)	2.00 (1.55)	<0.01
Drug allergies	1.82 (1.32)	2.31 (1.46)	<0.01
Failure of initial therapy	1.52 (0.93)	1.85 (1.02)	<0.05~~0.02~~
Mucoid P.aeruginosa	1.56 (0.85)	1.89 (1.46)	<0.01
Non-mucoid P.aeruginosa	1.98 (1.82)	2.19 (2.02)	<0.01
FVC (%)	47 (23)	56 (31)	<0.01
Drug allergies	49 (26)	60 (28)	<0.01
Failure of initial therapy	41 (12)	45 (17)	<0.05~~0.02~~
Mucoid P.aeruginosa	47 (26)	58 (33)	<0.01
Non-mucoid P.aeruginosa	46 (25)	51 (29)	<0.01
FEF25-75%	0.5 (0.47)	0.55 (0.76)	<0.01
Drug allergies	0.64 (0.62)	0.67 (0.71)	<0.05~~0.03~~
Failure of initial therapy	0.39 (0.36)	0.36 (0.54)	0.05
Mucoid P.aeruginosa	0.54 (0.47)	0.57 (0.49)	<0.05
Non-mucoid P.aeruginosa	0.5 (0.72)	0.5 (1.05)	<0.05

Data are expressed as median (IQR), because not normally distributed. Lung function is reported at start and end of treatment in the whole population and in the two cohorts.

The magnitude of the effect on FEV_1 was greater among the subjects with multiple drug allergies compared to those who failed the initial treatment (+0.25 L vs + 0.12 L, p<0.05). On the other hand, no difference in the magnitude of the improvement in FEV_1 was noted when comparing the cohorts identified based on the *P.aeruginosa* phenotype (data not shown).

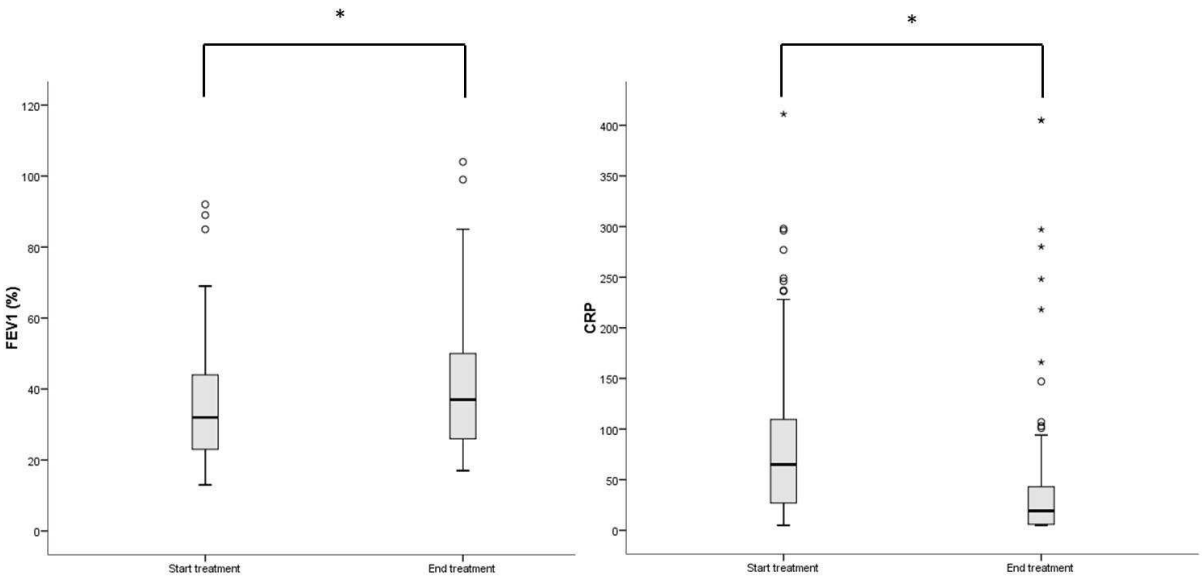

*Figure 1 Boxplot of FEV1 (%) and CRP at start and end of treatment. It shows median (horizontal bar), IQR (box) and 5-95th percentiles (bars). Circles are outliers and asterisks extreme outliers. * is* p*<0.05.*

Blood results

C-reactive protein (CRP) fell significantly on treatment both in the whole population and in each of the ~~two~~ cohorts based on reason to start treatment and *P.aeruginosa* phenotype (all $p<0.001$) (Fig 1) and no difference in the magnitude of this effect was noted depending on the reason to start treatment or *P.aeruginosa* phenotype (Table 3).

Table 3 Blood results at start and end treatment

	Start treatment	**End treatment**	***p***
CRP	65 (83)	19.3 (37.6)	<0.001
Drug allergies	53 (78)	12.2 (19)	<0.001
Failure of initial therapy	80 (120.5)	33 (64.7)	<0.001
Mucoid P.aeruginosa	38 (77.3)	12.2 (22)	<0.001
Non-mucoid P.aeruginosa	47 (56.6)	9 (15)	<0.001
Urea	4.4 (2.7)	4.4 (2.2)	ns
Drug allergies	4.7 (2.6)	4.6 (2.8)	ns
Failure of initial therapy	4.0 (2.5)	4.4 (1.8)	ns
Creatinine	52 (30)	51.5 (21)	0.006
Drug allergies	62 (27)	57 (23)	0.01
Failure of initial therapy	46 (24)	45 (25)	ns
ALT	16.5 (12)	20 (17)	<0.001
Drug allergies	18 (13)	24 (19)	<0.001
Failure of initial therapy	16 (9)	16.5 (8)	ns

Data are expressed as median (IQR), because not normally distributed. Blood results is reported at start and end of treatment in the whole population and in the two cohorts.
CRP is significantly lower at end of treatment compared to start. Creatinine showed a staitstically significant reduction at end IV in the whole population and among patients with multiple drug allergies. ALT increased significantly in the whole cohort and patients with drug allergies. Urea was similar at start and end of treatment.

Serum electrolytes, renal and liver function were monitored at start, mid and end treatment (Table 3). Urea was similar pre- and post-treatment. Creatinine level at end of treatment was similar to that at start of treatment. At mid treatment, creatine increased compared to baseline (Figure 2). This was above normal limit in 5% of cases and in 5 courses (4%) met the criteria for acute kidney injury, but renal function recovered at end of treatment. No clinically relevant difference in renal function was noted when taking into account the reasons to start fosfomycin, and concomitant treatment with colomycin and tobramycin (data not shown).

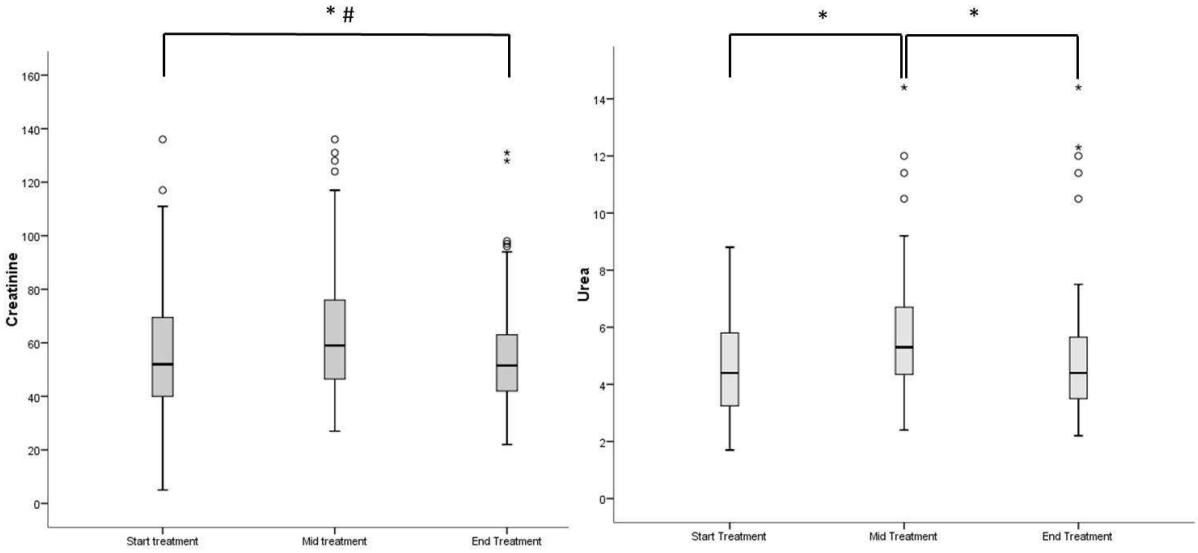

*Figure 2 Boxplot of creatinine and urea at start, mid and end of treatment. It shows median (horizontal bar), IQR (box) and 5-95th percentile (bars). Circles represent outliers and asterisks extreme outliers. * compares with mid treatment, # compares start vs end treatment. Creatinine increases significantly from start to mid, and then normalises again (*p*<0.001). Creatinine is statistically different at end compared to start (*p*=0.006), as it is lower. Urea increases at mid compared to start (*p*<0.001), and returns to baseline value at end (vs mid, *p*<0.001).*

Alanine aminotransferase (ALT) increased on treatment when comparing mid and post-treatment bloods with baseline (all $p<0.01$). This was above normal limits in 27% of cases.

Potassium, magnesium and phosphate decreased significantly on treatment (all $p<0.01$), requiring oral or IV supplementation was in 18%, 18% and 7.8% of cases, respectively.

Adverse events

Figure 3 summarises patients reported side effects. Nausea was the most common side effects (48.4% of cases) requiring an antiemetic in 43.4% of courses. Patients reported a worsened sense of constipation, increased bloating and lethargy whilst on fosfomycin compared to their previous experience with other antibiotics. Post-hoc analysis revealed that the patients who received fosfomycin following failure of initial treatment experienced more side effects than those with multiple drug allergies.

No allergic reactions to fosfomycin were recorded.

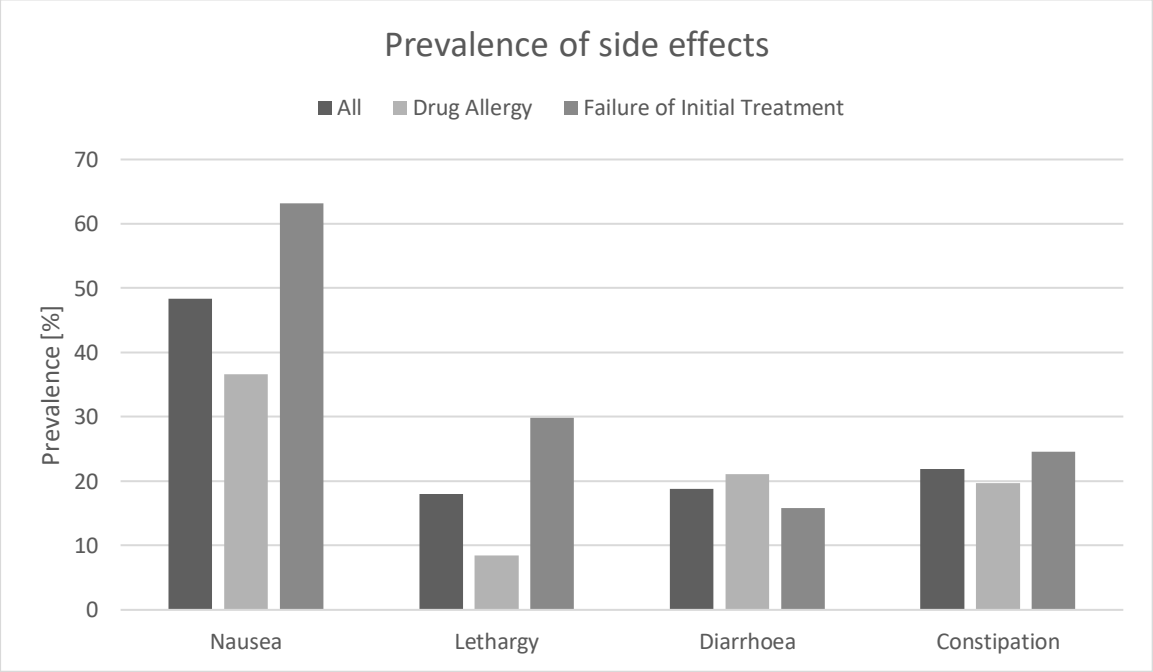

Figure 3 Prevalence of patients reported side effects in the whole population and in the two cohorts.

Discussion

To the best of our knowledge, this is the largest retrospective study assessing the use of IV fosfomycin in adult patients with CF. Our results highlight that antibiotics regimens including IV fosfomycin contribute to an improvement in lung function and reduction in CRP; appear to be safe, but can cause significant nausea, which was controlled with appropriate antiemetic cover. Limited data are available on the use of fosfomycin in combination with

other antibiotics to treat *P.aeruginosa* ~~-~~related pulmonary exacerbations in adult patients with CF.

~~and our~~ Our study supports and extends previous results, by showing that regimens including fosfomycin are effective independently of the reason to start this treatment and of the *P.aeruginosa* phenotype. In particular, we observed that both ~~in~~ patients with multiple drug allergies and ~~in~~ those who failed to respond to initial treatment had a significant increase in lung function on therapy, but this effect was greater for patients who had fosfomycin in combination regimens as first line treatment due to multiple drug allergies. This likely reflects an overall more stable clinical condition of these patients who had higher baseline lung function and lower inflammatory markers (data not shown).

Previous studies had shown that *in vitro* fosfomycin is more effective against mucoid *P.aeruginosa*. We did not observe any difference in clinical response depending on the phenotype of *P.aeruginosa*. In our practice~~, however,~~ we currently do not have routine testing for sensitivity to fosfomycin, which was prescribed, both initially and during following courses, empirically. The addition of susceptibility testing to fosfomycin would allow for better selection of patients to treat with regimens including this drug and potentially improve the outcome of treatment.

Fosfomycin is a unique antibiotic, which exerts its activity on a different synthetic pathway compared to other drugs. ~~and has a great synergistic effect with a variety of antibiotics. In our experience, patients were prescribed IV fosfomycin as part of a combination therapy which included beta-lactams, aminoglycosides, colomycin or ciprofloxacin.~~ Previous studies had shown that ~~fosfomycin~~ *in vitro* it has a synergistic effect against MDR *P.aeruginosa* when co-administered with beta-lactams[21], polymyxin B, tobramycin and ciprofloxacin[22,23]. It has been shown that, when used as a monotherapy, resistance to fosfomycin emerges rapidly. None of the~~se~~ antibiotic combinations studied *in vitro*, however, prevented the emergence of strains resistant to fosfomycin[22] and was influenced by the antibiotics susceptibility pattern of the strains[24]. In our experience, patients were prescribed IV fosfomycin as part of a combination therapy which included beta-lactams, aminoglycosides, colomycin or ciprofloxacin, depending on history of drug allergies, sensitivities and previous response to treatment. It would have been of interest to

analyse different outcomes depending on the antibiotic used in the combination treatment to identify the optimal regimen. We were, however, unable to perform this analysis since a sizeable part of our patients received more than one drug in combination with fosfomycin (i.e. colomycin and beta-lactam, aminoglycoside and beta-lactam). ~~In our practice, however, we do not have routine testing for sensitivity to fosfomycin, which was prescribed, both initially and during following courses, empirically.~~

In previous studies, fosfomycin has been shown to have a good safety profile without significant hepatic or renal impairment[15,18,20]. Our data show a statistically significant rise in the renal function, which however normalises at the end of treatment. Fosfomycin appeared to have a good safety profile even when administered with nephrotoxic drugs such as tobramycin and colomycin. The rise in creatinine was clinically significant, satisfying criteria for AKI (≥26 mmol/L compared to baseline) in 4% of courses. This rate is considerably lower compared to studies on tobramycin and colomycin, which showed an incidence of AKI up to 20% and 30% respectively [25,26].

Previous studies had shown that antibiotic regimens including fosfomycin are usually well tolerated with only a minor proportion of patients reporting gastrointestinal side effects, both among patients with CF[18–20] and in the general population[14,15]. In our study, however, a significant proportion of patients complained of nausea (approximately 50% vs 5% reported in literature) with need of antiemetic therapy in 43% of courses. In addition, constipation, bloating and diarrhoea were all reported in approximately 20% of courses of fosfomycin. These side effects may limit the tolerability of antibiotic regimens which include fosfomycin.

In our study, over half of the course of fosfomycin were given due to history of multiple drug allergies. None of the patient, however, develop an allergic reaction or an intolerance to fosfomycin.

The retrospective nature of this study, which included only patients who were receiving fosfomycin in combination therapy with other drugs, does not allow to discriminate which effects are strictly related to fosfomycin and what is due to the second antibiotics the

patients were receiving. As many subjects included in our study were on, or had been on, other antibiotics known to cause gastrointestinal side effects, the higher proportion of these adverse events compared to available literature could be a consequence of the other drug or an additive effect of both antibiotics. Similarly, the abnormality noted in the liver function results could be a consequence of the interaction of multiple antibiotics.

Despite having created two sub-groups of patients depending on the main reason to initiate regimens including fosfomycin, this study lacks ~~of~~ a control group to isolate the effects of ~~the~~ fosfomycin as add-on therapy.

~~Finally, t~~Treatment was started empirically as no sensitivity test to fosfomycin are available routinely in our Unit yet. Finally, this study reports a single-centre experience on the use of this antibiotic, with several patients receiving multiple courses of combination therapy including fosfomycin; caution should be therefore applied in generalising the validity of these findings which could be influenced by local pattern of susceptibility.

Further studies will be required to address these issues, and in particular, to establish if there is an optimal combination regimen with fosfomycin.

Conclusion

This large retrospective study shows that IV antibiotic regimens including fosfomycin are clinical effective, improve respiratory function and CRP. Multi-drug regimens which include fosfomycin appear to be safe. While nausea could be a significant side effects, it can be well controlled by regular prescription of anti-emetics. In view of our experience, we would recommend considering fosfomycin as a treatment option for patients with multiple drug allergies, or who failed to respond clinically to initial drug treatment.

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