International Journal of Antimicrobial Agents 43 (2014) 52–59

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria

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ARTICLE INFO

Article history:
Received 5 August 2013
Received in revised form
16 September 2013
Accepted 20 September 2013

Keywords:
Fosfomycin
PDR
XDR
Klebsiella
Pseudomonas
Critically ill

ABSTRACT

Fosfomycin is active in vitro against extensively drug-resistant (XDR) and pandrug-resistant (PDR) *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* carbapenemase-producing strains; however, the in vivo effectiveness against such pathogens is almost unknown. A multicentre, observational, prospective case-series study was performed in 11 ICUs. All consecutive fosfomycin-treated patients suffering from XDR or PDR fosfomycin-susceptible, microbiologically documented infections were recorded. Clinical and microbiological outcomes were assessed. A safety analysis was performed. In total, 68 patients received fosfomycin during the study period, 48 of whom were considered suitable for effectiveness analysis based on predefined criteria. Bacteraemia and ventilator-associated pneumonia were the main infections. Carbapenemase-producing *K. pneumoniae* and *P. aeruginosa* were isolated in 41 and 17 cases, respectively. All isolates exhibited an XDR or PDR profile, being fosfomycin-susceptible by definition. Fosfomycin was administered intravenously at a median dose of 24 g/day for a median of 14 days, mainly in combination with colistin or tigecycline. Clinical outcome at Day 14 was successful in 54.2% of patients, whilst failure, indeterminate outcome and superinfection were documented in 33.3%, 6.3% and 6.3%, respectively. All-cause mortality at Day 28 was 37.5%. Bacterial eradication was observed in 56.3% of cases. Fosfomycin resistance developed in three cases. The main adverse event was reversible hypokalaemia. In conclusion, fosfomycin could have a place in the armamentarium against XDR and PDR Gram-negative infections in the critically ill. Resistance development during therapy, which has been a matter of concern in previous studies, did not occur frequently. The necessity of combination with other antibiotics requires further investigation.

1. Introduction

The steadily increasing nightmare of antimicrobial resistance worldwide, and in particular the emergence of extensively drug-resistant (XDR) and pandrug-resistant (PDR) strains of *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*, along with the current shortage of new antimicrobials has led to the revival of old antibiotics such as colistin and fosfomycin [1]. Despite the rather successful clinical experience with colistin [2], ultimately resistance development is reported, particularly among *K. pneumoniae* strains, attributed to its expanding nosocomial use [3,4]. On the other hand, fosfomycin, an antibiotic of the 1970s, whilst active in vitro against carbapenemase-producing *P. aeruginosa* (CPPA) and *K. pneumoniae* (CPKP) strains, is almost totally unexplored in XDR infections [5]. This lack of evidence, along with anecdotal reports of fosfomycin administration in Greek

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http://dx.doi.org/10.1016/j.ijantimicag.2013.09.010

intensive care units (ICUs), led the Hellenic Society of Chemotherapy (HSC) to organise this multicentre, prospective, observational study. The aims were: (i) the description of clinical and epidemiological characteristics of patients receiving fosfomycin for XDR and PDR infections; (ii) the depiction of current treatment strategies; and (iii) the disclosure of treatment outcomes using predefined criteria.

2. Patients and methods

2.1. Description of the study

This was a prospective case-series study organised by the HSC's 'Infections in the ICU' Working Group. A steering committee of the protocol was designated, and contact was made with centres that expressed an interest in participating. Finally, 15 centres agreed to participate and local investigators were assigned. The time frame of the study was set between 1 January 2010 and 30 June 2012. During this period, fosfomycin was prescribed at least once in 11 ICUs and all of them provided data. They consisted of mixed medical-surgical ICUs, both academic and non-academic, located in the metropolitan area of Athens (8 ICUs), Thessaloniki (1 ICU) and Epirus region (2 ICUs).

2.2. Patient enrolment and populations

All adult, critically ill patients admitted to study centres were enrolled in the study if they received at least one intravenous dose of fosfomycin disodium. We tried to recruit consecutive cases by appointing local investigators to continuously monitor patient charts and pharmacy records in order to track all patients receiving fosfomycin. Furthermore, the complete registration of patients was assured by the fact that fosfomycin disodium is not commercially available in Greece and its administration requires a laborious procedure through the Ethics Committee of each hospital and the National Institute of Pharmaceutical Research and Technology.

Enrolled patients were suitable for the safety analysis and comprised the 'safety population'. To characterise the outcomes of fosfomycin treatment against XDR and PDR infections, those patients suffering from fosfomycin-resistant or non-XDR/PDR infections, those with an unclear diagnosis (i.e. those not meeting specific infection criteria) and those receiving fosfomycin for <72 h were excluded from the effectiveness analyses, and thus the 'effectiveness population' was formed.

2.3. Definitions

Types of infections were defined according to the US Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) criteria [6], whilst the Surviving Sepsis Campaign definitions of 2008 [7] were used for characterisation of the septic status of patients. Pandrug resistance was arbitrarily defined as resistance to all available antimicrobials with the exception of fosfomycin, and extensive drug resistance was defined as resistance to all available antimicrobials except fosfomycin plus colistin and/or tigecycline. These definitions are in essential concordance with subsequently proposed terminology [8], with the exception of fosfomycin susceptibility not being considered in our designation. Early fosfomycin administration was defined as the initiation of fosfomycin ≤24 h from infection onset.

2.4. Recorded data

Data were collected anonymously for each patient and included: demographic characteristics; co-morbidities; reason for ICU admission; disease severity both at entrance and at fosfomycin initiation as determined by Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores; presence of invasive devices; current antimicrobial treatment at the time of fosfomycin initiation; co-administered antimicrobials; site of infection; isolated micro-organisms and their susceptibility pattern; results of subsequent cultures of relevant biological samples; and sequential haematology and biochemistry results.

2.5. Microbiology and culture procedures

Blood cultures were performed with a BacT/ALERT® 3D system (bioMérieux, Marcy-l'Étoile, France). Bronchial secretion cultures were quantitatively performed and were considered positive when growth was $\geq 10^6$ CFU/mL [9]. A positive urine culture from a Foley catheter required $\geq 10^3$ CFU/mL. Strain identification and antimicrobial susceptibilities were performed with the VITEK® 2 system (bioMérieux) and were interpreted in accordance with Clinical and Laboratory Standards Institute (CLSI) standards [10]. Regarding tigecycline, susceptibility was determined by Etest (AB BIODISK, Solna, Sweden) and was interpreted according to the breakpoints approved by the US Food and Drug Administration (FDA) [11]. For fosfomycin in particular, Etest strips containing 25 μg of glucose-6-phosphate in addition to fosfomycin were applied [10]. Fosfomycin minimum inhibitory concentrations (MICs) were interpreted according to the CLSI as follows: susceptible, ≤64 μg/mL; intermediate, 128 μg/mL; resistant, ≥256 μg/mL. All isolated *P. aeruginosa* and *K. pneumoniae* strains were screened for carbapenemase production by phenotypic tests [12] followed by PCR by applying specific primers [13].

2.6. Outcomes

The primary endpoint was clinical and microbiological outcomes in the effectiveness population. A test-of-cure visit was performed on Day 14 from fosfomycin initiation, during which a clinical and microbiological outcome was ascribed to each patient by the local investigator. Clinical outcome was judged as: (i) successful, if all signs of infection resolved; (ii) failure, if the infection persisted or relapsed; (iii) superinfection, if a new infection with a new pathogen emerged; and (iv) indeterminate, if the outcome could not be classified to one of the above categories. Microbiological outcome was considered as: (i) eradication, if the initial pathogen was eradicated from relevant cultures; (ii) persistence, if the original pathogen persisted or relapsed; and (iii) indeterminate, if it could not be reliably classified to one of the above categories, e.g. in the case of absence of subsequent relevant cultures.

Secondary outcomes included all-cause mortality at Days 14 and 28, manifestation of toxicities and in vivo development of resistance during the 28-day interval. Resistance development was deemed to have occurred when a specific strain's MIC surpassed the threshold of 64 μg/mL during the treatment course of the index infection. An identical sensitivity pattern for all agents except fosfomycin was used as a criterion of sameness of the micro-organism.

2.7. Subgroup analysis

Post hoc subgroup analyses were performed regarding type of infection, the presence of severe sepsis/septic shock, the resistance profile of the pathogen (i.e. XDR vs. PDR) and the timing of fosfomycin initiation (i.e. early vs. late).

2.8. Safety analysis

Treating physicians and local investigators followed the safety population for the development of adverse events daily.