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Short communication

Clinical evaluation of subcutaneous administration of cefepime☆

Évaluation de l'administration du céfépime par voie sous-cutanée

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ABSTRACT

Objectives. – Cefepime is a fourth-generation cephalosporin active against *Pseudomonas aeruginosa* and most Enterobacteriaceae. Intravenous (IV) administration is the standard route of prescription. However, subcutaneous administration (SC) may represent an interesting alternative. We aimed to evaluate SC administration of cefepime versus the IV route in geriatric patients.
Patients and methods. – Multicenter retrospective analysis in patients treated with cefepime by SC route who underwent plasma concentration monitoring.
Results. – Twelve patients were included in the SC group and matched to 12 patients in the IV group. The median and mean C_{min} levels were 29.05 mg/L [14.2–48.2]; 33.4 mg/L (±21.8) in the SC group and 31.9 mg/L [26.5–51.7]; 39.6 mg/L (±27) (*P* = NS) in the IV group. No local SC administration-related complications were reported. No relapse was observed over six months of follow up.
Conclusion. – Subcutaneous use of cefepime seems to have the same clinical and microbiological effectiveness as parenteral administration.

1. Introduction

Subcutaneous administration is frequently used in geriatric medicine, especially for hydration, antalgics, and antibiotic therapies. This approach is convenient, with a lesser risk of local complications, especially in patients with few available veins for infusion. Among third- and fourth-generation cephalosporins, only ceftriaxone has already been assessed with this route of administration. Cefepime is a fourth-generation cephalosporin active against *Pseudomonas aeruginosa* and most Enterobacteriaceae, even when natural cephalosporinase (AmpC) is overproduced [1]. Walker et al. evaluated a 30-minute infusion by subcutaneous (SC) administration in 10 healthy adult volunteers [2]. Their results showed a pharmacokinetic profile similar to that of an intramuscular injection with excellent tolerability and acceptability. We aimed to clinically evaluate SC administration of cefepime versus the intravenous route in geriatric patients using drug monitoring.

2. Methods

We performed a retrospective study including all patients who experienced drug monitoring of cefepime plasma levels, administered subcutaneously between January 1, 2014 and December 31, 2017. All included patients were matched on weight, age, glomerular filtration rate, and dosing regimen with patients hospitalized in the same ward and treated with cefepime administered intravenously. Dosing regimens were adapted to the renal function in both groups. For the subcutaneous route, cefepime was reconstituted in 50 mL of 0.9% NaCL and administered over 10 to 30 minutes. Plasma samples for drug monitoring were obtained at the steady state and plasma concentrations of cefepime were measured by UHPLC-ESI-HRAM (high resolution accurate mass, Orbitrap Exactive, Thermo Fisher) using the Therapeutic Monitoring of Anti-infective Drug platform, at Paris Saint-Joseph Hospital. Target attainment was defined as 100% T > MIC and T > 4 MIC (percentage of time during a dosing interval that the drug concentration

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Table 1
Clinical and biological data of all patients receiving subcutaneous versus intravenous cefepime (univariate analysis).

	Total	IV group*N* = 12 (%)	SC group*N* = 12 (%)	*P*
Men/women	11/13	5/7	6/6	1
Mean age (years)	79.8 (± 16.2)	79.1 (± 15.8)	80.6 (± 17.1)	
> 75 years (*N*, %)	18 (75)	9 (75)	9 (75)	1
Mean weight (kgs)	75.5 (17.6)	75.4 (± 17.4)	76.9 (± 22.7)	0.88
Mean glomerular filtration rate (mL/min)	68.3 (± 31.3)	67.8 (± 28.5)	69.6 (± 33.2)	0.97
< 30 mL/min	5 (20.8)	3 (25)	2 (16.7)	
Mean dose (g/day)	3.2 (± 1.9)	3.3 (± 1.9)	3.1 (± 1.8)	0.75
Mean Charlson score	4.6 (± 1.1)	4.1 (± 1.1)	5.1 (± 1.2)	0.85

exceeded the MIC or 4 times the MIC of the causative agent) and were compared between the SC and IV groups of patients. We used the cefepime breakpoint of 1 mg/L for Enterobacteriaceae and 8 mg/L for *P. aeruginosa* [3].

The following data was retrospectively collected from five centers for which we performed dosages for their patients: mode of administration, dosing regimen, renal function with calculation of glomerular filtration rate estimated by the Modification Diet in Renal Disease (MDRD) formula, site of infection, type of bacteriological sampling performed, identified bacteria, pharmacological data (dose, duration, number of injections), empirical or documented indication, clinical outcome, and death.

Results of the descriptive statistical analysis were presented as means ± SD for quantitative variables. The number of patients and the associated percentages were used for qualitative variables. Secondly, qualitative variables were compared with Chi^2 test. Quantitative variables were compared between the two groups with Student's *t* test. The threshold of significance was set at 5% for all tests performed.

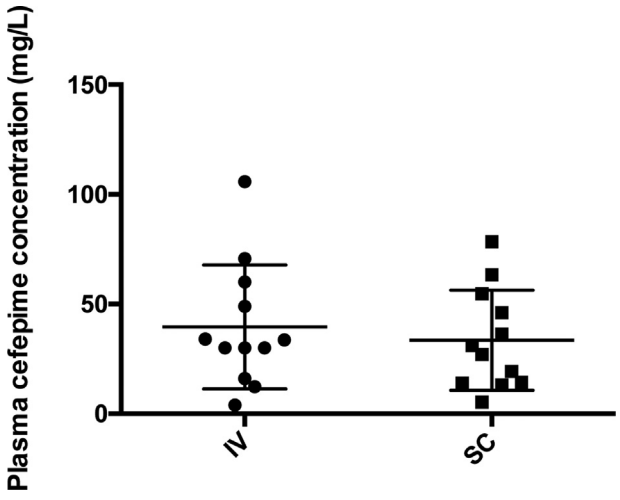

Fig. 1. Plasma cefepime concentration between intravenous and subcutaneous treatment groups.

3. Results

Twelve patients were treated with cefepime by subcutaneous administration during the study period. The median age of patients was 86 years [range: 74–90]. The median weight was 78.4 kg [range: 52–86]. Eight patients had renal failure with creatinine clearance < 60 mL/min. Ten patients were treated for bone and joint infections and two for bloodstream infections related to urinary tract infections. Bacterial documentation only revealed Gram-negative bacilli infections (five due to naturally producing AmpC-Enterobacteriaceae, six due to *P. aeruginosa*, and one with multiple bacteria). These patients were compared with 12 patients chosen according to matching criteria, but treated by intravenous administration. The Table 1 presents the epidemiological data of both groups of patients and compares them. No significant differences were observed between the two groups. The average dose was 3.3 g/day (± 1.8) in the intravenous group versus 3.1 g/day (± 1.8) in the subcutaneous group. It was most often a monotherapy (20 patients; 83.3%) while in few cases cefepime was associated with aminoglycosides (four patients, 16.7%) with no differences between the SC and IV groups. The median and mean of C_{min} levels were 29.1 mg/L [range: 14.2–48.2] and 33.4 mg/L (± 21.8) in the SC group, and 31.9 mg/L [range: 26.5–51.7] and 39.6 mg/L (± 27) (*P* = NS) in the IV group, respectively (Fig. 1). Considering the threshold of cefepime for Enterobacteriaceae (1 mg/L) and for *P. aeruginosa* (8 mg/L), all patients included in this study had a residual plasma cefepime concentration that exceeded the threshold of the isolated bacteria. Moreover, 85% of them had a C_{min} greater than four times the threshold. No local complications related to the subcutaneous administration were reported. All patients had positive clinical outcome with no relapse over a six-month follow-up period.

4. Discussion

There are several reasons for using subcutaneous administration in weaker patients: a difficult venous access (poor venous network, etc.), risks related to venous access (infection, extravasation), difficulty to maintain the venous access especially in patients presenting with cognitive or behavioral disorders (agitation, wandering) [4,5]. There is little published data on antibiotic therapy even though the subcutaneous approach is commonly used in geriatrics. Ceftriaxone, ertapenem, and teicoplanin are among the few antibiotics for which subcutaneous administration has been extensively studied [6–11].

To the best of our knowledge, this is the first study evaluating the pharmacokinetics of subcutaneous administration of cefepime in patients. Our results are in agreement with those reported in a previous study performed with healthy volunteers, showing that a single dose of SC cefepime administration resulted in a plasma concentration profile similar to a single dose of intramuscular cefepime administration [2]. C_{min} data for subcutaneous administration was compared with data obtained with intravenous administration and interestingly the results were similar, irrespective of the patients compared. Moreover, no local or systemic adverse effects attributable to cefepime administration were reported and signs of infection disappeared by the end of the treatment duration. Our case series is one of the largest in geriatric patients receiving cefepime and particularly with subcutaneous administration [12]. However, the retrospective design of our study could have induced a bias by loss of information on data collection, especially for the analysis of data determining prescription for subcutaneous injections such as swallowing or behavioral disorders. Indeed, the evaluation of cognitive disorders was not performed systematically.

Subcutaneous administration of cefepime did not seem to worsen the prognosis of patients, as there was no significant difference in the rate of clinical cure.

5. Conclusion

Subcutaneous use of cefepime seems to have the same clinical and microbiological effectiveness as parenteral administration and could facilitate the implementation of early outpatient treatment and management of populations with limited access such as the geriatric population. These results need to be confirmed in a prospective multicentric study including a larger population.

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Contributions

BP: study concept and design, data analysis, preparation of article.

AM: acquisition of data and preparation of article.

GP: acquisition and interpretation of data, preparation of article.

ALM: study concept and design, preparation of article.

NEH: study concept, interpretation of data, preparation of article.

Disclosure of interest

The authors declare that they have no competing interest.

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