Ceftazidime Dosage Recommendations in Burn Patients: From a Population Pharmacokinetic Approach to Clinical Practice via Monte Carlo Simulations

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ABSTRACT

Background: Ceftazidime dosage regimen recommendations based on pharmacokinetic/pharmacodynamic approaches are not available for burn patients.

Objective: The goal of this study was to propose a continuous dosage regimen of ceftazidime in burn patients, taking into account different MICs and pharmacokinetic covariates.

Methods: The population pharmacokinetic analysis was conducted by using software dedicated to the analysis of nonlinear mixed effects models. The population pharmacokinetic model was first developed and validated in 70 adult burn patients. Taking into account various MICs of pathogens, 3 Monte Carlo simulation trials were conducted by using target concentration intervals (10–100, 20–100, and 40–100 mg/L). The recommended dosages were defined as the minimum dose leading to the highest percentage of patients whose ceftazidime concentrations were included in the target interval.

Results: Serum creatinine and age were identified as covariates of ceftazidime clearance. Age was also involved in volume of distribution. The simulations showed that a dose of 6 g/d did not allow achievement of the target interval in most patients. Regardless of dosage regimen, age, and serum creatinine, the mean percentage of patients reaching the 10- to 100-mg/L and the 20- to 100-mg/L target intervals were 99.4% (0.3%) and 96.1% (0.8%), respectively. For the 40- to 100-mg/L target interval, this percentage was only 76.4% (2.1%) (range, 65%–80%).

Conclusions: Age and serum creatinine level can be used at the bedside to determine the initial doses of ceftazidime. These Monte Carlo simulations highlight the need of a reappraisal of ceftazidime's use in burn patients. Doses between 3 and 16 g/d are proposed, taking into account the pathogens' MICs. However, for sepsis caused by a pathogen with an MIC ≥ 8 mg/L, an insufficient percentage of burn patients will reach the therapeutic target with the recommended dosages. (*Clin Ther*. 2013;35:1603–1612) © 2013 Elsevier HS Journals, Inc. All rights reserved.

Key words: burn, ceftazidime, dosage regimen, Monte Carlo simulations, pharmacokinetics.

INTRODUCTION

Severe *Pseudomonas aeruginosa* infection can jeopardize the prognosis for burn patients and necessitates rapid antibiotic therapy. Among the antibiotics available, ceftazidime may be an appealing choice because of its lower risk of resistance compared with most β-lactams.[1,2]

Ceftazidime pharmacokinetics are defined by high renal excretion and a volume of distribution similar to that of the extracellular space.[3] It is mainly eliminated by glomerular filtration, and 88% of the dose is recovered in the urine over 24 hours. Consequently, changes in renal function in the hypermetabolic phase after a burn injury affect the pharmacokinetics of ceftazidime,[4,5] and a 2-g dose every 8 hours may be inadequate in burn or intensive care unit (ICU) patients.[6]

For β-lactams, bacterial killing is primarily related to time that concentrations in the tissues and plasma

Accepted for publication August 23, 2013.
http://dx.doi.org/10.1016/j.clinthera.2013.08.014
0149-2918/$ - see front matter

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exceed a certain threshold.[7] Dosing regimens are therefore being re-evaluated to keep plasma concentrations above certain thresholds over the whole treatment period, regardless of the administration schedule.[8] Because ceftazidime exhibits time-dependent killing of gram-negative bacteria in vitro or in critically ill patients, studies involving continuous administration of cephalosporin confirm that the steady-state blood concentration should be in excess of the bacterial MIC.[7,9] Continuous infusion optimizes the pharmacodynamics of β-lactams by providing adequate antibacterial activity over the 24-hour dosing period with a reduction in the total daily dose of the antimicrobial agent.[10–12]

Some studies have reported an influence of covariates such as age, creatinine, or creatinine clearance on ceftazidime disposition in burn patients.[4,6,13] Two studies used a population approach[5,14] without any validation process. Therefore, a recommended ceftazidime dosage regimen based on a pharmacokinetic/pharmacodynamic approach is not actually determined in such singular burn patients. The aim of the present study was to propose an a priori–required dosage of ceftazidime given by continuous infusion to this population. Its estimation is based on clinical and biological parameters used in our practice at the bedside of burn patients.

MATERIALS AND METHODS

Two prospective, open-label, randomized population studies of ceftazidime's pharmacokinetics were conducted in burn patients, adhering to the agreement of the Toulouse and Lyon Ethical Committees. The clinical parts of the studies were performed in the burn patient units of the University Hospital in Toulouse-Rangueil (n = 50) and of the Hospital "St Joseph et St Luc" in Lyon (n = 20). The Toulouse population's data have been partially used in previous studies.[4–6] Written informed consent was obtained from the patients or their relatives.

All the ceftazidime plasma concentration data were obtained and analyzed in the Laboratoire de Pharmacocinétique et Toxicologie Clinique of the Purpan Hospital in Toulouse, France.

Patients

Patients were studied during the secondary phase of their burn injuries. The following demographic, clinical, and biological parameters were collected as possible covariates: age, sex, weight, height, mechanical ventilation, serum creatinine, proteins, and blood urea nitrogen. Specific burn indices such as Baux, UBS, Tobiasen, and burn area were also recorded. The glomerular filtration rate was estimated from creatinine clearance, calculated by using the Cockcroft-Gault method[21] and the Modification of Diet in Renal Disease (MDRD).[22]

Drug Administration

Antibiotics were prescribed for local infections or for sepsis either empirically when a patient's condition required immediate treatment or after a bacteriologic evaluation. Before inclusion, patients were randomized to treatment according to the mode of administration: continuous infusion of ceftazidime with a loading dose or discontinuous administration. Seventy patients entered into these studies between 2003 and 2009, and they received ceftazidime by 3 modes of administration. One group received a ceftazidime dose of 6 g/d in 3 separate 20-minute infusions of 2 g each every 8 hours (n = 25). The second group was given 6 doses of 1 g each every 4 hours (n = 25). A trough concentration was measured at the end of day 1; the frequency and/or the dose of ceftazidime was then adjusted to obtain a target trough concentration if necessary. The new dosing schedule could be increased to 1 g 8 times a day (ie, every 3 hours), or reduced to 1 g 4 times a day (ie, every 6 hours) or to 1 g 3 times a day (ie, every 8 hours). The third group received 8 g on day 1, a 2-g loading dose over 30 minutes followed by 6 g/d continuously administered (n = 20). This dosage was initially adapted in patients with an impaired renal function according to the usual recommendations (summary of product characteristics).

Blood Sampling and Measurements

In the fractionated administration groups, blood was sampled in dry tubes at 24, 24.33, 48, and 48.33 hours after the beginning of the treatment. In the continuous infusion group, patients were randomly distributed in 3 subgroups, and blood was sampled at 0, 0.25, 1.5, 6, and 24 hours or 0.5, 2, 12, and 24 hours or 1, 4, 18, and 24 hours. When the dosing regimen was changed for monitoring reasons, further samples were taken to determine the new ceftazidime concentrations. A total of 286 measurable serum concentration were available.

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