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ORIGINAL ARTICLE

Variability of pharmacokinetic parameters in patients receiving different dosages of daptomycin: is therapeutic drug monitoring necessary?

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Abstract Pharmacokinetic studies of daptomycin in septic patients indicate that pharmacokinetic parameters may be altered. The purpose of this clinical investigation is to determine the pharmacokinetics of daptomycin in a population of hospitalized patients with clinically significant gram-positive infections and receiving daptomycin. Daptomycin was measured using an isocratic HPLC technique. Thirty-five patients suffering from gram-positive severe infections and receiving daptomycin were included in the study. Patients were divided into two groups, depending on the dose of daptomycin received: group A, including 24 patients receiving 6 mg/kg/day daptomycin and group B, 11 patients receiving 8 mg/kg/day. Patients receiving a daptomycin dosage of 8 mg/kg/day had significantly higher values of mean C_{max} and AUC_{0-24}. Each group was further divided into three subgroups, according to the creatinine clearance (CrCl) values: (1) patients with a CrCl >80 ml/min, (2) patients with CrCl ranging between 80 and 40 ml/min, and (3) patients with CrCl <40 ml/min. Compared to patients with normal renal function, those with CrCl <40 ml/min had higher mean values of minimum concentration (C_{min}) ($p < 0.001$), AUC_{0-24} ($p = 0.03$), and prolonged plasma half-time ($p < 0.001$). These differences were present both in patients receiving 6 and those with 8 mg/kg/day. However, in each of the three subgroups with different degrees of renal function a marked variability of pharmacokinetics parameters was observed. The factors associated with increased mortality were an infection acquired in the ICU, hypoalbuminemia, and AUC/MIC <666. The marked variability that characterizes daptomycin pharmacokinetics in these patients suggest the monitoring of the main pharmacokinetic parameters in this clinical setting.

Keywords Daptomycin · Pharmacokinetic · Therapeutic drug monitoring · Staphylococcal infections · AUC/MIC

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Introduction

Gram-positive pathogens, especially *Staphylococcus aureus* and coagulase-negative staphylococci, are a common cause of nosocomial infection, especially bloodstream infections (BSI) and skin or soft tissue infections (SSTI) [1–6]. Daptomycin, a lipoglycopeptide antibiotic with bactericidal activity against gram-positive organisms, may be prescribed for patients with severe SSTI, BSI, or infectious endocarditis (IE) [7–11].

Hospitalized patients with severe infection usually have many comorbidities, including reduction of renal function, hypoalbuminemia, or obesity; in addition, sepsis can lead to acute kidney injury and the need for renal replacement therapy. Optimal antibiotic dosing ensuring therapeutic concentrations is essential to reduce the risks of therapeutic failure and the development of antibiotic resistance. Considering that sepsis has a high mortality in critically ill patients with acute kidney injury, optimizing antibiotic

dosing is crucial in this patient population. In these cases, because daptomycin is eliminated primarily by the kidneys, dose adjustments are required [12, 13]. On the other hand, drug accumulation and excessive antibiotic concentrations can result in an increased risk of adverse events, such as creatine kinase elevation with rare cases of rhabdomyolysis.

Daptomycin pharmacokinetics has been extensively studied in animal models and healthy volunteers [14]. However, studies conducted in septic patients with or without chronic kidney disease indicate that pharmacokinetic parameters may be altered [15, 16], especially in some circumstances such as critical illnesses, severe sepsis, or acute kidney injury. The purpose of this clinical investigation is to determine the pharmacokinetics of daptomycin in a heterogeneous population of hospitalized patients with clinically significant gram-positive infections, to correlate PK/PD parameters with the outcome of these patients.

Materials and methods

Patient sample and data collection

The study was carried out in the Policlinico Umberto I of Rome, during a period from November 2009 to December 2010. Thirty-five patients were enrolled; the decision to start daptomycin therapy was based on the personal decision of the attending physician or the infectious diseases consultant. The following parameters were collected for each patient: demographics, clinical and laboratory findings, microbiological data, duration of daptomycin therapy, side effects, and outcome. A written consent from the patient was obtained in all cases. The study was approved by the independent ethics committee or institutional review board of the participating centers.

Inclusion criteria

Patients who fulfilled the following criteria were eligible to participate in this study: (1) they had to be men or women 18 years of age or older, and (2) they had positive blood cultures for gram-positive cocci before final identification or a documented infection with another gram-positive pathogen.

Exclusion criteria

Patients were not eligible for participation in the study if any of the following criteria were met: (1) they had a known allergic reaction to daptomycin or product excipients; (2) they had suspected meningitis or osteomyelitis; (3) they were known to be infected with a daptomycin-resistant organism or a gram-negative organism and did not yet meet the criteria for the addition of antimicrobial therapy for the treatment of an infection caused by a gram-positive organism; (4) they had been treated with daptomycin or other antibiotic agents covering gram-positive organisms in the preceding 7 days; (5) they were pregnant, were positive for serum human chorionic gonadotropin, or were lactating; (6) they were on hemodialysis or continuous ambulatory peritoneal dialysis; (7) they had rhabdomyolysis or a history of rhabdomyolysis; (8) they had documented or suspected pneumonia caused by a gram-positive organism; (9) they had signs and symptoms of myopathy with an elevation of the creatine-phosphokinase (CPK) level (approximately five times the upper limit of normal).

Dosing and sample collection

Daptomycin (Novartis Pharma) was infused intravenously over 30 min. A dosage of 6 or 8 mg/kg every 24 h was based in consideration of patient weight and the type of infection. Blood samples for measurement of plasma daptomycin concentrations were collected before the first administration of the dose (predosing); at 0 min, 30 min (end of infusion), and at the following times after the start of infusion: 1, 2, 4, 8, 12, and 24 h from the first administration.

Pharmacokinetic study

Blood samples (5 ml) were collected in heparinized syringes, separated by centrifugation, kept at −80 °C, and sent to the Department of Pharmacology of University of Florence for further analysis. Concentrations of daptomycin in plasma were determined by a validated high performance liquid chromatography (HPLC) in plasma with a Pinnacle II C8 column (5 μm 250 × 4.6 mm) and measured by UV detection ($l = 220$ nm). The mobile phase consisted of ammonium phosphate (0.5 %) and acetonitrile mixed in a 66:34 (vol/vol) ratio. An injection volume of 100 μl was selected, and the flow rate was maintained at 1.5 ml/min. A standard curve ranging from 1.56 to 50 mg/l was selected, and linearity was confirmed by linear regression ($r^2 = 0.9994$). The intrarun ($n = 6$) coefficients of variation (CVs) were 0.1 mg/l for the low concentration and 50 mg/l for the high concentration.

Quality controls were 6.4 and 2.6 %, respectively. The interrun ($n = 6$) CVs for the low-concentration (0.1 mg/l) and the high-concentration (80 mg/l) quality controls were 2.9 and 2.8 %, respectively. The lower limit of detection was 0.1 mg/l.

Samples were prepared by mixing 500 μl specimen with 1 ml acetonitrile. The samples were mixed and centrifuged