Case Report of a Successful Treatment of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Bacteremia and MRSA/Vancomycin-Resistant *Enterococcus faecium* Cholecystitis by Daptomycin

Carlo Tascini,1† Antonello Di Paolo,2†* Marialuisa Polillo,2 Mauro Ferrari,3 Paola Lambelet,4 Romano Danesi,2 and Francesco Menichetti1

Infectious Diseases Unit, Santa Chiara University Hospital, Pisa, Italy1; Division of Pharmacology, Department of Internal Medicine, University of Pisa, Pisa, Italy2; Division of Vascular Surgery, Department of Oncology, Transplants and New Technologies in Medicine, University of Pisa, Pisa, Italy3; and Division of Medicine, Versilia Hospital, Camaiore, Italy4

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A 72-year-old man, receiving 8 mg daptomycin/kg body weight/day for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, was diagnosed with MRSA/vancomycin-resistant *Enterococcus faecium* (VRE) cholecystitis (daptomycin MIC values, 1 and 2 mg/liter, respectively). After the fifth drug dose, the bile concentration of daptomycin was 66 mg/liter 5 min after drug administration, with the biliary concentration/MIC values higher than 30 for both bacterial strains. Therefore, daptomycin achieved therapeutic levels in bile, hence suggesting a role for the drug in the treatment of MRSA/VRE cholecystitis.

Gram-positive bacteria are often responsible for severe and difficult-to-treat infections, characterized by high mortality rates in hospital settings (3), but the introduction of daptomycin has represented a step forward for the treatment of those severe infections sustained by drug-resistant strains, such as methicillin-resistant *Staphylococcus aureus* (MRSA) (4) and vancomycin-resistant *Enterococcus* spp. (5). The drug has a concentration-dependent activity, and its effectiveness is best predicted by the ratio among MIC values and maximum plasma concentration (C\text{max}/MIC) or area under the time-concentration curve (AUC/MIC) values (8).

Daptomycin is characterized by linear pharmacokinetics in healthy volunteers up to doses of 12 mg/kg body weight once a day (1), but maximum plasma concentrations in patients could be lower than those measured early in volunteers (2). The drug is not a substrate of liver metabolism, and it is primarily excreted via the kidneys as an unmodified molecule (1); it is highly bound to plasma proteins (>90%) and has a limited volume of distribution (approximately 0.1 to 0.2 liters/kg of body weight). Daptomycin displays a limited penetration into the central nervous system (7), even if it rapidly distributes to subcutaneous adipose and bone tissues (10), and achieves adequate concentrations in vitreous humor (9).

In the present study, we describe the case history of a male patient affected by MRSA bacteremia and MRSA/vancomycin-resistant *Enterococcus faecium* (VRE) cholecystitis who received daptomycin. Because the measurement of drug levels was available, we also reported plasma and bile concentrations of the drug. The local ethics committee gave the approval for the review of the patient’s clinical data (protocol no. 55945, 24 September 2009). A 72-year-old man with exacerbation of chronic obstructive pulmonary disease (COPD) was admitted to the intensive care unit (ICU) and intubated. Because of the occurrence of central venous catheter (CVC)-related MRSA bacteremia, he was treated with 8 mg teicoplanin/kg/day (MIC, 1 mg/liter). One week after his discharge to home, he was again admitted to the emergency department for a dissecting aneurysm of the abdominal aorta, which was promptly treated by surgery. Blood culture was positive for a probable hetero-VISA (vancomycin-intermediate *S. aureus*) strain (MIC values, measured with Etest, for vancomycin and teicoplanin were 2 and 8 mg/liter, respectively), while the hetero-VISA phenotype was suggested by growth of a heteroresistant subpopulation inside the Etest ellipse, when a macro Etest was performed according to the manufacturer’s instructions (bioMérieux, Marcy L’Etoile, France). Therefore, daptomycin (MIC, 1 mg/liter) was administered to the patient as a 30-min intravenous (i.v.) infusion at the dose of 8 mg/kg/day (total dose, 525 mg/day). At the same time, a cholecystitis occurred, and in order to improve the treatment of the infection, a biliary drainage was applied. In the presence of granulocytes during the Gram stain, a VRE strain susceptible to daptomycin (MIC, 2 mg/liter) and a MRSA strain with the same susceptibility pattern of the blood isolate were identified in the bile.

Five days after the beginning of daptomycin administration, when steady state was presumably achieved, two blood samples were obtained 30 min before and 5 min after drug infusion through a peripheral vein access. Blood was collected into heparinized tubes, and plasma was obtained by centrifugation. At the same time points, two samples of bile obtained from biliary drainage were collected (approximate volume, 0.5 ml),
and in all four samples daptomycin concentrations were measured using a high-performance chromatographic method (6). Briefly, plasma and bile were extracted with methanol, and clear supernatants were analyzed in a Waters Breeze apparatus (Waters, Milford, CT) equipped with a Waters 2476 UV detector set at 214 nm. The elution of samples was obtained isocratically through a base-deactivated silica C8 Hypersil chromatographic column, 250 mm by 4.6 mm by 5 μm (Phenomenex, Torrance, CA), using an acetonitrile-phosphate buffer mobile phase. Results demonstrated that bile concentrations of daptomycin before and after drug administration (22 and 66 mg/liter, respectively) were superimposable with those found in plasma at the same time points (27 and 66 mg/liter, respectively), and the highest values of the bile concentration/MIC ratio were 66 and 33 in the case of the MRSA and VRE strains, respectively. Clinical conditions and signs of the infection improved rapidly, while daptomycin was continued for 60 days until biliary drainage was removed. Echographic examination after the catheter removal demonstrated no abscess formation. Blood cultures remained negative for the entire period of daptomycin therapy, and no signs or symptoms of myopathy were observed during lipopeptide administration despite the relatively high predose concentration, which could be associated with an increased risk of toxicity.

Plasma concentrations of daptomycin were in agreement with those previously reported for the same dose levels (2) and associated with good clinical and microbiological cure rates. More than 38 to 68% of a daily daptomycin dose is excreted unmodified by the kidneys (1), but in the present patient bile concentrations were nearly identical to those measured in plasma at the same time points. Although biliary excretion of the drug accounts for only 3% of the total daily dose, the small volume of secreted bile seemed to ensure high daptomycin concentrations. In fact, the ratio between the highest bile concentration of the drug and the VRE MIC for daptomycin was greater than those previously reported (8), suggesting that the drug could have a role, even if partially, in the microbiological eradication of VRE.

In conclusion, daptomycin was effective in treating MRSA bacteremia, while it could improve the treatment of the MRSA/VRE cholecystitis, due to the achievement of high concentrations into the bile. The present results warrant further evaluation of daptomycin for the treatment of biliary tree infections.

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REFERENCES