Safety of High-Dose Intravenous Daptomycin Treatment: Three-Year Cumulative Experience in a Clinical Program

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(See the editorial commentary by Cosgrove and Corey on pages 181–3)

Background. There are limited safety data for high-dose and long-term daptomycin treatment (>6 mg/kg administered for ≥14 days). We present our experience in 61 patients.

Methods. We performed a retrospective chart review for all patients treated with daptomycin at New York Hospital Queens (Flushing) from 1 January 2004 through 30 April 2007; patients were identified through a computerized hospital pharmacy database.

Results. Sixty-one patients (29 male and 32 female patients; mean age, 66.6 years) received a mean dose of 8 mg/kg of daptomycin for a median of 25 days (range, 14–82 days). Twelve patients (with bone and skin and soft-tissue infections) did not have an identified microbiologic isolate. Gram-positive infections included bloodstream infection with or without infective endocarditis (n = 32), skin and soft-tissue infection (n = 14), bone and joint infection (n = 9), and intra-abdominal infection (n = 5), and unidentified infection (n = 1). Prosthetic devices were removed from 11 of 20 patients. Grade 1 adverse events occurred in 22 patients and did not lead to daptomycin discontinuation. Fifty-eight patients underwent creatine phosphokinase (CPK) analysis (34 patients had paired CPK analyses at the beginning of and during therapy, and 13 patients had random CPK analysis performed during treatment). Three patients had constitutional and/or musculoskeletal symptoms accompanying CPK levels 1–10 times upper limit of normal (grade 3). All occurred after 24 days of treatment and improved after daptomycin treatment was discontinued. Two of 3 patients were morbidly obese (body mass index grade III).

Conclusions. Daptomycin treatment was well tolerated at a mean dose of 8 mg/kg for a median duration of 25 days. The incidence of symptomatic CPK level elevation was within the range reported with lower doses of daptomycin and/or for shorter treatment durations.

Daptomycin is a novel lipopeptide antibiotic with a unique mechanism of action against gram-positive bacteria that provides potent in vitro bactericidal activity [1–3]. It is approved at a dose of 4 mg/kg for the treatment of complicated skin and soft-tissue infection (SSTI) and at a dose of 6 mg/kg for Staphylococcus aureus bloodstream infection (BSI), including treatment of right-sided endocarditis. Clinical experience with doses >6 mg/kg is limited, but data reported to date suggest that daptomycin is safe and well tolerated at higher doses [4–11]. On the basis of the drug’s pharmacokinetic profile and concentration-dependent killing, higher doses may be beneficial in treating severe infections. We describe our safety experience with clinical use of daptomycin at doses >6 mg/kg for courses of ≥14 days.

METHODS

We conducted a retrospective chart review for all patients treated with daptomycin at New York Hospital Queens (Flushing) from 1 January 2004 through 30 April 2007. The review was approved by the local institutional review board, and patient consent was not
required. Patients were included in the study group if they received daptomycin at doses ≥6 mg/kg for ≥14 days. Eligible patients were identified via computerized hospital pharmacy database, and clinical data were collected from their medical records, including age, sex, comorbid conditions, clinical diagnosis, microbiologic isolate identification and antibiotic susceptibility, indication for daptomycin use, use of sequential or concurrent antibiotics, dose and duration of daptomycin treatment (including duration of outpatient completion of course), adverse clinical events, and creatine phosphokinase (CPK) levels. Body mass index (BMI) was calculated for all patients as the weight in kilograms divided by the square of the height in meters.

Safety was defined as adverse events documented in the medical record. Adverse events were compared with those reported in the package insert and with those published in a randomized study of daptomycin for the treatment of staphylococcal BSI and were graded 1–4 [12–14]. Significant elevation in CPK level was defined by increases in serum CPK values 10-fold greater than the upper limit of normal, with or without accompanying musculoskeletal symptoms. Daptomycin dosing was based on mg per kg of actual body weight, and the intervals used were in accordance with the manufacturer’s recommendations (i.e., every 24 h for creatinine clearance >30 mL/min and every 48 h for clearance <30 mL/min) [12]. Creatinine clearance was calculated using the Cockcroft-Gault formula at baseline and periodically throughout the course of therapy, and renal insufficiency was defined as creatinine clearance <30 mL/min. In addition, hospital policy requires discontinuation of concomitant 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA)-reductase inhibitors when daptomycin is initiated to avoid confusion regarding potential etiology of CPK elevation.

Infections were categorized as uncomplicated BSI, complicated BSI, infective endocarditis, complicated SSTI, bone and joint, intra-abdominal, and unidentified infections. Definitions of uncomplicated BSI, complicated BSI, and infective endocarditis were consistent with those used in published studies [13]. Complicated SSTIs included abscesses, postsurgical wound infections, infected ulcers, and cellulitis due to gram-positive cocci without concurrent BSI, as defined elsewhere [15]. Empirical use of daptomycin was defined as administration of treatment to a patient with signs and symptoms of infection without an identified source or microbiologic isolate. Patients with concurrent pneumonia did not receive daptomycin as the sole active agent. Prosthetic devices included catheters (e.g., venous, arterial, and hemodialysis), intracardiac devices (e.g., pacemakers, defibrillators, and ventricular assist devices), prosthetic cardiac valves, prosthetic joint replacements, intravascular grafts, tissue expanders, and nonabsorbable mesh. BMI was calculated for all patients, and obesity was defined as grade I (30–34.9), grade II (35–39.9), and grade III (≥40) [16].

RESULTS

Sixty-one patients met the inclusion criteria. Of these, 32 were female and 29 were male; the mean age was 66.6 years. The mean duration of hospital stay among the study group was 29.2 days (median, 21 days; range, 6–148 days). Nineteen patients (31.1%) were admitted from long-term care facilities, and 42 (68.9%) were admitted from home. Renal insufficiency was found in 20 patients (32.8%).

Sixty-one patients were distributed among the 7 categories of defined infections, as follows: uncomplicated BSI (7 patients), complicated BSI (19; 4 of 11 patients underwent removal of prosthetic device), left-sided infective endocarditis (6; 2 of 3 patients underwent removal of prosthetic device), complicated SSTI (14; all 3 underwent removal of prosthetic devices), bone and/or joint infections (9; 1 of 2 prosthetic joints were removed), intra-abdominal infection (5), febrile neutropenia (1; empirical treatment was administered). Twelve patients did not have an identified microbiologic isolate (7 of 14 patients with complicated SSTI, 3 of 9 patients with bone and joint infections, 1 of 5 patients with intra-abdominal infection, and the single patient who received empirical daptomycin for neutropenic septicemia). Organisms treated included methicillin-resistant S. aureus (16 patients), methicillin-susceptible S. aureus (2), methicillin-resistant Staphylococcus epidermidis (3), Enterococcus faecium (9), Enterococcus faecalis (9), group B streptococcus (1), and unidentified organism (12).

Patients received a mean dose of 8 mg/kg (range, 7–11 mg/kg). A dose of 11 mg/kg in 1 patient was corrected later to 8 mg/kg on the basis of actual body weight reassessment. All patients included in the analysis received a minimum of 14 days of daptomycin treatment with a median of 25 days of treatment (range, 14–82 days). Thirteen patients were inadvertently administered doses greater than intended because of an initial miscalculation of actual body weight (8 patients) or because of delayed correction for reduced creatinine clearance (5 patients). BMI calculation revealed grade 1 obesity in 45 of 61 patients and grade III obesity in the remaining 16 patients.

Three of 61 patients did not undergo any CPK evaluation before or during daptomycin therapy (these patients remained asymptomatic and completed their treatment courses). Of the remaining 58 patients, 41 underwent CPK analysis within 72 h after initiation of therapy. Thirty-four (83%) had paired CPK analysis (an initial CPK analysis within 72 h after initiation of therapy and a follow-up CPK analysis during therapy). Another 17 patients underwent CPK analysis either before or during treatment.

Of 61 patients, 22 experienced grade 1 adverse events while receiving therapy (i.e., anemia, diarrhea, nausea, hypokalemia,
and arthralgias) and did not require discontinuation of daptomycin treatment. In addition, 3 of 61 patients (all receiving 8 mg/kg of daptomycin) became symptomatic with constitutional and/or musculoskeletal complaints after 24–28 days of treatment. Grade 3 CPK level elevations (levels >1000 U/L) were present in all 3 patients. Daptomycin treatment was discontinued, and patients had resolution of symptoms. One of the 3 patients underwent follow-up CPK level analysis several weeks later, and the patient’s CPK level returned to within normal range. Two of the 3 patients were obese (BMI grade III). The other 13 patients with grade III BMI did not experience any adverse events.

**DISCUSSION**

Daptomycin is a rapidly bactericidal antibiotic with activity against gram-positive cocci. It demonstrates concentration-dependent killing, in vitro synergy with a number of other antibiotics, and in vitro penetration into biofilm [2, 17–21]. Our dose selection and use of daptomycin was based on these properties, available safety data, and evidence of serious or poorly controlled infection.

In vitro studies of simulated endocardial vegetations with susceptible and nonsusceptible strains of *S. aureus* treated with simulated daptomycin doses of 6 mg/kg and 10 mg/kg in combination with gentamicin and rifampin have demonstrated rapid bactericidal activity of all doses against susceptible *S. aureus*. There is an increased rate of killing at the higher dose, improved activity with combination therapy against a majority of drug-susceptible strains, and improved activity even against some of the nonsusceptible strains [22]. The concern of decreasing daptomycin susceptibility in the face of ongoing bacteremia and/or subtherapeutic dosing has been raised [13, 23].

To date, there are limited safety data for clinical use of daptomycin in doses >6 mg/kg [4–11]. In general, daptomycin is well tolerated, with few significant adverse events other than CPK level elevation. The largest clinical study used daptomycin 6 mg/kg for treatment of bacteremia and right-sided infective endocarditis in 120 patients, compared with standard of care treatment [13]. CPK level elevations occurred in 6.7% of patients treated with daptomycin, compared with <1% of patients treated with a comparator drug [13]. CPK level elevation led to discontinuation of daptomycin treatment for 3 (2.5%) of 120 patients; none of the patients treated with a comparator discontinued treatment. Four patients in the daptomycin arm were considered to be obese (Cubist Pharmaceuticals, unpublished data).

A recent report of a pilot study of the treatment of complicated SSTI that used higher dose daptomycin (10 mg/kg for 4 days) demonstrated an overall incidence of CPK level elevation of 8.3% (4 of 48 patients); 3 patients experienced symptomatic CPK level elevation of >500 U/L [9]. A retrospective report of Cubist Pharmaceuticals’ ongoing registry of patients receiving >8 mg/kg of daptomycin noted a discontinuation rate of 2.1% associated with treatment-related adverse events [10]. In that cohort, 18 (19%) of 94 patients received doses ≥10 mg/kg (48% of all patients treated for bacteremia, including infective endocarditis), and 3 patients experienced a CPK level increase (2 required treatment discontinuation) at doses of 8–10 mg/kg.

The current report represents a large cumulative clinical case series of patients who received daptomycin at a mean dose 8 mg/kg for a median duration of 25 days. The majority of the patients had infections due to methicillin-resistant *S. aureus* or methicillin-resistant *S. epidermidis* in the context of complicated BSI and in the presence of various prosthetic devices. Discontinuation of daptomycin treatment because of grade 3 adverse events occurred in 3 of 61 patients in our cohort, with an overall incidence of 4.9%. Two of the 3 patients were considered to be obese, although obesity has not been described to date as a risk factor for daptomycin-related CPK level elevation or myositis. Several small studies (including a complicated SSTI trial) examined multiple parameters in obese patients receiving daptomycin and did not demonstrate increased toxicity [4, 15].

Significant CPK level elevation in our cases was found in 3 of 34 patients who underwent paired CPK analysis and 3 of 47 patients who underwent any CPK analysis (8.8% and 6.4%, respectively). Clinical studies to date report an incidence of significant CPK level elevation of 2.5%–8.3% (Cubist Pharmaceuticals, unpublished data) [9, 13]. It is not clear from our cohort whether our CPK level elevation is an effect of the higher dosing regimen or the inconsistent performance of CPK levels.

Limitations of this report include a small cohort of patients, incomplete and inconsistent CPK analysis, and variable dosing intervals because of a cumulative learning curve (i.e., use of higher doses because our experience with daptomycin supported safety parameters at higher doses). A later analysis is planned to analyze outcomes in all patients treated with daptomycin in our cumulative 3-year experience.

We recommend further study of higher-dose daptomycin use in larger cohorts with consistent CPK analysis. Our experience suggests that most patients are symptomatic when significant CPK level elevations occur. Additional studies using higher doses of daptomycin administered to obese individuals for prolonged periods would be beneficial to delineate whether this parameter is associated with increased toxicity.

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