INTRODUCTION

Daptomycin (Cubicin for Injection, Cubist) is a cyclic lipopeptide derived from the fermentation of Streptomyces roseosporus. It has in vitro spectrum of activity against gram-positive aerobic organisms, such as Staphylococcus aureus, Enterococcus faecalis, and Enterococcus faecium. Daptomycin binds to bacterial membranes and causes a rapid depolarization of membrane potential. As a consequence, this inhibition of protein, DNA, and RNA synthesis results in bacterial cell death. At the time of our evaluation, daptomycin at a dose of 4 mg/kg per day was approved by the Food and Drug Administration (FDA) for infections caused by complicated skin and skin structure infections resulting from S. aureus (including methicillin-resistant isolates), Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, and E. faecalis (vancomycin-susceptible isolates). The therapeutic use of daptomycin in treating bacteremia, endocarditis, and other severe infections caused by methicillin-resistant S. aureus (MRSA) and vancomycin-resistant enterococci (VRE) remained under investigation by the FDA.

In June 2004, daptomycin was officially added to the formulary at our hospital along with guidelines for its use. In addition to the guidelines, the use of daptomycin was permitted only after it was approved by the Antimicrobial Management Team and after consultation with an infectious-disease specialist. The P&T committee recommended a follow-up audit of annual usage. The hospital’s 2004 guidelines can be summarized as follows:

Daptomycin should not be used for:

- treatment of pneumonia, surgical prophylaxis, or empirical coverage.

STUDY OBJECTIVES

Our primary objective was to determine whether daptomycin use met the P&T committee’s approved guidelines. Secondary objectives were:

- to determine the number of patients who had received previous therapy with vancomycin, linezolid, or quinupristin/dalfopristin (Synercid, Monarch) before switching to daptomycin.
- to describe the infection and the organism for which daptomycin was prescribed.
- to describe the daptomycin dosage regimen, including doses based on milligrams per kilogram of body weight.
- to determine whether the dosage interval was appropriate for patients according to their renal function status.

METHODS

We performed a retrospective descriptive chart review after obtaining approval from the institutional review board. We identified patients for inclusion via a computerized report generated for all patients who had received daptomycin between December 2003 and December 2004. After the chart review was completed, the data were collated in a Microsoft Access database and analyzed in Epi Info. We also generated a computerized report to compare antibiotic usage trends for daptomycin, linezolid, and parenteral vancomycin. We depicted antibiotic measurement on the basis of the World Health Organization’s definition of defined daily doses (DDDs).2

RESULTS

Daptomycin was prescribed for 44 patients during the study period. The mean ± standard deviation (SD) age was 58.6 ± 16.5 (range, 22–90) years; 22 patients were men, and 22 were women. Forty-one patients (93.2%) were white, two patients (4.5%) were African-American, and one patient (2.3%) was Hispanic. The mean ± SD length of stay was 27.4 ± 26.4 days (range, 1–120 days; median, 17.5 days).

Of the 44 patients, 32 (72.7%) met the drug usage guidelines and three (6.8%) did not; nine (20.5%) did not meet the specific guidelines, but we considered this to be clinically appropriate.

Of the 32 cases for which the guidelines were appropriate, 15 cases were for the treatment of resistant gram-positive infections in patients who were allergic to vancomycin or lin-

Disclosure: Since 2005, Dr. Tompkins has been the principal investigator at Allegheny General Hospital for the Cubicin Outcomes Registry and Experience (CORE) for the treatment of serious gram-positive infections protocol, sponsored by Cubist Pharmaceuticals.
ezolid; 12 cases were for the treatment of resistant gram-
positive infections resistant to linezolid; and five cases were for
the treatment of resistant gram-positive infections in patients
who developed thrombocytopenia thought to be secondary to
linezolid or in patients with existing thrombocytopenia if lin-
ezolid use was a concern.

Of the three patients not meeting the guidelines, one patient
was treated for an empyema, and two patients were treated empirically with daptomycin: one of these two patients had a
urinary tract infection (UTI) and the other had sepsis with pneumonia. The patient with the UTI received one dose of dap-
tomycin overnight. After a consultation with an infectious-
disease specialist the following day, daptomycin was dis-
continued. An infectious-disease consultation was obtained
for all 44 patients, resulting in 100% compliance.

Thirty-eight patients (86.4%) had previously been treated
with vancomycin; 15 of these 38 patients (39.5%) were consid-
ered intolerant to vancomycin, as judged by the physician, at
the time daptomycin was prescribed. The median length of
vancomycin therapy before the initiation of daptomycin was 10
days (range, 1–28 days).

Of the 38 patients, eight (21%) were considered by the physi-
cian to have an inadequate response to vancomycin. The
median length of vancomycin therapy was 14 days (range,
5–42 days).

Of the 44 patients, 24 (54.5%) had received linezolid previ-
ously. Of the 24 patients, eight (33.3%) were intolerant to lin-
ezolid at the time daptomycin was prescribed. The median
length of linezolid therapy was four days (range, 2–14 days).

Of the 24 patients, four (16.7%) were considered to have an
inadequate response to linezolid. The median length of lin-
ezolid therapy was six days (range, 1–10 days).

Other vancomycin and linezolid exposures included either
(1) an earlier history of intolerance to vancomycin or linezolid
or (2) another reason, such as a change from vancomycin
because of a resistant organism (e.g., VRE). No patients had
received quinupristin/dalfopristin earlier (Figure 1).

Daptomycin was prescribed for bacteremia in 13 patients
(29.5%); skin and skin structure infections in 10 (22.7%); osteo-
myelitis in four (9.1%); endocarditis in four (9.1%); sepsis in five (11.4%); and other infections in four (9.1%).

At the initiation of therapy, targeted organisms included
MRSA in 18 patients (40.9%); VRE in 11 (25%); methicillin-
resistant *Staphylococcus epidermidis* (MRSE) in five (11.4%); and other infections in 10 (22.7%); the latter consisted of two
cases each of methicillin-susceptible *S. aureus* (MSSA), methi-
cillin-susceptible *S. epidermidis* (MSSE), Enterococcus species, or empirical therapy with no positive
culture identified.

Of the 44 patients, eight had a second gram-positive organ-
ism of concern: VRE in three patients; *Enterococcus* species in
two patients; and a history of MRSA, MSSE, or VRE in one
patient each.

The mean dosage was 336.8 ± 114.3 mg (range, 200–600 mg)
or 4.4 ± 1.1 mg/kg (range, 1.9–6 mg/kg) (Table 1). The mean
weight was 86.8 ± 24.8 kg (range, 45.4–150 kg).

Daptomycin was prescribed every 24 hours for 34 patients
(77.3%), every 48 hours for nine patients (20.5%); and after each
hemodialysis for one patient (2.2%). The mean creatinine clear-
ance (CrCl) ± SD was 54.6 ± 32.4 mL/minute (range, 4–129
mL/minute). We used the Cockcroft–Gault equation to calcu-
late CrCl.

Thirty-two patients (72.7%) had a CrCl of 30 mL/minute or
more, and 12 patients (27.3%) had a CrCl of less than 30
mL/minute. Therefore, the initial dosage interval was appro-
priate for 42 patients (95.5%) and inappropriate for two
patients (4.5%). In one patient with an inappropriate dosage
interval, the dose was changed to the appropriate interval
before the second dose was administered. The median length of
inpatient therapy was 6.9 ± 6.3 days (range, 1–28 days). The
median was five days.

Twenty-one patients (47.7%) were discharged home with
daptomycin. The mean total length of therapy, including out-
patient therapy, was 22.2 ± 18.3 days (range, 1–56 days). The
median was 14 days.

A baseline creatinine kinase (CK) was obtained for nine
patients (20.9%), and all baseline values were within normal
limits. Among patients whose CK levels were being monitored, no
patients experienced increased CK concentrations during their
hospitalization.

Hypotension secondary to sepsis occurred in one patient
who was receiving daptomycin. This patient had previously
received vancomycin and rifampin for a nonhealing MRSA
wound infection. Because of the potential reaction to dapto-
mycin, the patient was subsequently switched to linezolid.

The quarterly usage of IV vancomycin at baseline (July to
September 2003) was 62.5 defined daily doses (DDDs) per

<table>
<thead>
<tr>
<th>Daptomycin Dose (mg/kg)</th>
<th>No. of Patients (%)</th>
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<tbody>
<tr>
<td>Below 4</td>
<td>6 (14%)</td>
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<tr>
<td>4</td>
<td>23 (53.3%)</td>
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<tr>
<td>4.5–4.9</td>
<td>2 (4.6%)</td>
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<tr>
<td>6</td>
<td>12 (27.9%)</td>
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* Based on the patient’s total body weight.
DISCUSSION

Overall, the use of daptomycin met most of our institution’s drug-usage guidelines; it was used primarily for treating multidrug-resistant, gram-positive infections. Because of its in vitro activity against resistant gram-positive infections such as VRE and MRSA, daptomycin has been described in the literature as a welcome addition for antibiotics with gram-positive activity.3,4 Daptomycin was also prescribed for other off-label infections (e.g., for endocarditis at the time of the evaluation), which prompted a dose higher than 4 mg/kg.

Sakoulas et al. compared the efficacy of daptomycin with that of vancomycin, each with or without rifampin, in a model of experimental aortic valve endocarditis resulting from MRSA in Sprague-Dawley rats.5 This in vivo experimental model of MRSA endocarditis demonstrated that daptomycin, when given at a dose corresponding to a human dose of 4 to 6 mg/kg every 24 hours, was comparable to or better than therapy with vancomycin; the combination of rifampin with daptomycin was also superior to daptomycin alone.

At the time of our data collection, ongoing studies were under way at a dose of 6 mg/kg per day in humans. On May 25, 2006, the FDA granted approval for daptomycin 6 mg/kg per day for the treatment of S. aureus bacteremia, including right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates.6 Subsequently, the S. aureus Endocarditis and Bacteremia Study Group published the data for IV daptomycin 6 mg/kg daily, compared with standard therapy for bacteremia and endocarditis caused by S. aureus.7

Standard therapy consisted of vancomycin 1 g every 12 hours with appropriate dose adjustments or an anti-staphylococcal penicillin, such as nafcillin (Unipen, Wyeth), oxacillin, or flucloxacillin (Floxapen, Fluclox) at 2 g every four hours. A successful outcome was documented in 44.2% (53 of 120 patients) in the daptomycin group compared with 41.7% (48 of 115 patients) receiving standard therapy (absolute difference, 2.4%; 95% confidence interval [CI], −10.2% to 15.1%). Daptomycin was associated with a higher rate of microbiologic failure (19 patients) compared with standard therapy (in 11 patients) ($P = 0.17$). Fowler et al. thus concluded that daptomycin was not inferior to standard therapy for S. aureus bacteremia or right-sided endocarditis.7

In the Cubicin Outcomes Registry and Experience (CORE) 2004 database, 126 of 168 patients who had bacteremia and were clinically evaluable received daptomycin. The median initial dose was 4 mg/kg (range, 2.5–9.2 mg/kg).8 The overall clinical success rate was 89%.

For patients with endocarditis (n = 49), the median initial dose was 6 mg/kg (range, 4–7 mg/kg). Levine and Lamp concluded that daptomycin should be considered a possible therapy for patients with right-sided S. aureus endocarditis, although further investigation was needed for those patients with left-sided or enterococcal endocarditis.8

In our audit, microbiological or clinical cure rates were not available from all patients, primarily because these patients were frequently discharged to the outpatient setting on daptomycin and data were not available when therapy was finally completed.

In the CORE 2004 database, 67 patients were treated for osteomyelitis and were clinically evaluable at the end of therapy.10 The median initial dose was 5.6 mg/kg (range, 3.2–7.5 mg/kg). The clinical success rate was higher with an initial daptomycin dose of more than 4 mg/kg, compared with an initial dose of 4 mg/kg or less (88% vs. 65%; $P = 0.013$).10 In our evaluation, three of the four patients received a dose of 4 mg/kg, and one patient received 6 mg/kg. All four patients completed daptomycin therapy as outpatients.

For most of our patients, the daptomycin dosage interval was adjusted appropriately for patients with renal insufficiency. Of note, the dosage based on weight (mg/kg) varied widely, but it did not exceed 6 mg/kg per dose.

The package insert for daptomycin describes pharmacokinetic data for six moderately obese patients with a body mass index (BMI) of 25 to 39.9 kg/m² and six extremely obese patients with a BMI of 40 kg/m² or greater.8 After a dose of 4 mg/kg IV based on total body weight, daptomycin plasma clearance was approximately 15% lower in the moderately obese subjects and 23% lower in the extremely obese subjects, compared with non-obese controls. The area-under-the-curve (AUC₀–∞) concentration increased by approximately 30% in the moderately obese subjects and by 31% in the extremely obese subjects. Thus, no dosage adjustment is warranted in obese patients, according to this package insert.5

The variety of dosages in our evaluation might have

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resulted partly because of the site of concern; for example, the usual dose of 4 mg/kg was not prescribed for a UTI, based on the extensive renal excretion of daptomycin.

Pai et al. noted that administering daptomycin based on total body weight in morbidly obese patients correlated best to the volume of distribution.11 They also reported a case in which vancomycin serum concentrations were used to estimate a dosing interval for daptomycin in a morbidly obese patient with renal insufficiency.12 They found that using vancomycin serum concentrations was more accurate, compared with using common CrCl equations, for estimating CrCl.

Daptomycin has been studied in healthy volunteers at doses exceeding the current FDA-approved dosages. The pharmacokinetics and tolerability of daptomycin at 10 mg/kg once daily for 14 days, 12 mg/kg once daily for 14 days, or 6 or 8 mg/kg once daily for four days were evaluated in 12 participants.13 All of the patients had BMIs ranging from 24 to 27 kg/m² and weights ranging from 53 to 72 kg. No electrocardiographic abnormalities or electrophysiological evidence of muscle or nerve toxicity was noted, and none of the patients experienced myalgia.

The most common adverse events were headache (27.8%), adenoviral upper respiratory infection (22%), aphthous stomatitis (11.1%), constipation (11.1%), arthralgia (11.1%), and UTIs (11.1%). All of these events, except arthralgia and UTI, were also observed in one or more patients who received placebo.

Although one patient receiving daptomycin 10 mg/kg on the third day of therapy had mild numbness in the hands, this event did not recur despite continuation of therapy. One patient receiving 12 mg/kg experienced mild paresthesia on the fourth day, but this event subsequently resolved seven days later, even with continued therapy.13

We did not observe any creatinine phosphokinase (CPK) elevations in our audit, but we recognize that myopathy can occur. Because CPK elevations were more frequent in the phase 1 and 2 trials, when daptomycin was given more often than once daily, this agent should not be administered more than once per day. In the phase 3 skin and skin structure trial, CPK elevations were reported in 15 of 534 patients (2.8%) at a dose of 4 mg/kg every 24 hours. In the bacteremia/endocarditis trial, Fowler et al. reported CPK elevations in eight of 120 patients (6.7%) who received 6 mg/kg every 24 hours.7

In one case report, a 26-year-old patient receiving daptomycin 6 mg/kg per day for 14 days experienced muscle pain with a creatinine kinase (CK) increase to 492 units/liter.14 Rhabdomyolysis was also reported in a 45-year-old woman with refractory acute myeloid leukemia who received 6 mg/kg every 24 hours.15

The most recent daptomycin package insert (from 2007) recommends that patients be monitored for symptoms of muscle pain or weakness, especially in the distal extremities.16 CPK levels should be monitored weekly or more often in patients who have recently received other drugs or who are taking statin drugs concomitantly. For patients with renal insufficiency, CPK levels and renal function should be monitored more often. Daptomycin should be discontinued if patients have myopathy as well as CPK elevations above 1,000 units/liter (about five times the upper limit of normal [ULN]) or if asymptomatic patients have CPK levels above 2,000 units/liter (10,000 times the ULN or greater).16

In addition to concerns about adverse drug events, reduced susceptibility to daptomycin has been associated with less susceptibility to vancomycin (i.e., vancomycin minimum inhibitory concentrations [MICs] of 4 to 16 mcg/mL) in S. aureus isolates. The S. aureus isolates submitted to the Centers for Disease Control and Prevention (CDC) revealed an association of vancomycin MICs of 4 mcg/mL or 8 mcg/mL with daptomycin MICs of 2 mcg/mL or greater.17

According to the Clinical and Laboratory Standards Institute (CLSI), daptomycin MICs of 1 mcg/mL or lower in Staphylococcus isolates are considered to be susceptible.18 In another report, resistance occurred in a patient with vancomycin-resistant E. faecalis infection.19 The initial three isolates of E. faecalis had daptomycin MICs of 1 mcg/mL before the patient started daptomycin therapy. A fourth isolate obtained during therapy had an increased daptomycin MIC of 16 mcg/mL.19 Decreased susceptibility or treatment failure has also been reported in other cases of S. aureus infection.20–22

We presented the results of our evaluation to the P&T committee, and vancomycin remains the empirical antibiotic of choice for S. aureus infections at our institution. When culture and sensitivity data are available, de-escalation to a narrower-spectrum antibiotic is recommended (e.g., nafcillin for MSSA). The P&T committee recommended that the hospital’s daptomycin guidelines be reworded as follows:

Revised Daptomycin Drug Usage Guidelines: Daptomycin requires ID consultation and approval by the Antimicrobial Management Team.

Daptomycin is indicated for:

- treatment of resistant gram-positive infection (e.g., MRSA, VRE) in patients who are allergic to vancomycin or linezolid.
- treatment of resistant gram-positive infection (e.g., MRSA, VRE) that is intermediate or resistant to vancomycin and resistant or intermediate to linezolid.
- treatment of resistant gram-positive infection (e.g., MRSA, VRE) in patients who develop thrombocytopenia thought to be secondary to linezolid or patients with existing thrombocytopenia where use of linezolid would be concerning (clinical judgment must be used).
- treatment of gram-positive infection in patients who have not responded to treatment with vancomycin.

Daptomycin should not be used for: treatment of pneumonia, surgical prophylaxis, or empirical coverage.

CONCLUSION

Guidelines for daptomycin usage, along with a requirement of consultation with an infectious-disease specialist, have succeeded in ensuring that prescribing is appropriate at our hospital. Although daptomycin use increased during the audit period, the overall use of vancomycin and linezolid remained constant. It is anticipated that reserving daptomycin as an alternative agent for serious gram-positive infections will limit...
the emergence of resistance to cyclic lipopeptide antibiotics and will preserve this agent’s role in the antimicrobial armamentarium against bacterial infections.

REFERENCES