Use Of Daptomycin In The Treatment Of Prosthetic Joint Infections: A Prospective Observational Study Of 30 Patients With Infected Prosthetic Joint Infections

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Citation

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Abstract

This prospective, observational study evaluated daptomycin, a lipopeptide antibiotic active against most Gram-positive bacteria, in prosthetic joint infections. Thirty patients received daptomycin for a mean of 37 days. Most patients received daptomycin 4 or 6 mg/kg/day as second- or third-line therapy after failing prior therapy; three patients with reduced renal capacity at baseline received 4 mg/kg q48h. At 6 to 12 months' posttreatment follow-up, 20 patients (66%) had no clinical, laboratory, or radiographic signs of recurrent infection. Ten patients (33%), all of whom were infected with methicillin-resistant Staphylococcus aureus, failed therapy with daptomycin. Daptomycin was discontinued in one patient due to an elevated level of creatinine phosphokinase. These results suggest daptomycin is a viable alternative to vancomycin or vancomyin-containing combination regimens for prosthetic joint infections.

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INTRODUCTION

A novel cyclic lipopeptide, daptomycin has been shown to have in vitro bactericidal activity against antibiotic-resistant Gram-positive bacteria such as methicillin-resistant Staphylococcus aureus (MRSA), glycopeptide intermediate S. aureus (GISA), methicillin-resistant Staphylococcus epidermidis (MRSE), and vancomycin-resistant enterococci (VRE) [1–4], pathogens for which there are limited therapeutic alternatives. Daptomycin has a novel mechanism of action, binding to bacterial membranes and causing a rapid depolarization of membrane potential that results in inhibition of protein, DNA, and RNA synthesis, leading to cell death [5,6]. The drug's antimicrobial activity against staphylococci is concentration-dependent and rapidly bactericidal [3,7,8]. No cross-resistance of daptomycin with other classes of antibacterials has been reported [9–11]. Treatment-emergent resistance in S. aureus is infrequent but has been reported [12–14], and S. aureus isolates exhibiting reduced susceptibility to vancomycin may also exhibit higher minimum inhibitory concentrations (MICs) to daptomycin [15–17]. Daptomycin is approved in the United States for the treatment of complicated skin and skin structure infections (cSSSI) at 4 mg/kg once daily and for S. aureus bacteremia (including right-sided endocarditis) at 6 mg/kg once daily [18].

Despite the large volume of successful replacement surgeries for hip, knee, shoulder, and elbow joints, prosthetic joint infection (PJI) is a relatively rare but devastating complication associated with significant morbidity and health care utilization costs. Approximately 60% of PJIs occur by direct contamination during the operative procedure [19]. Rates of PJI range from 0.5–1.0% for hip replacements, 0.5–2% for knee replacements, and < 1% for shoulder replacements [20–22]. In addition to lengthy hospital stays, surgical interventions and antimicrobial therapy add to the patient's risk of further complications and disability [23,24]. The pathogenesis of PJIs is influenced by microorganisms adhering to each other to form a biofilm, a process mediated by the polysaccharide intercellular adhesion encoded by the ica operon [25]. Biofilm formation occurs consistently as a consequence of host protein deposition on the prostheses, which serve as ligands for bacterial receptors [26]. An animal model of S. aureus infection in implanted tissue cages found that the presence of

the foreign body decreased the minimal infecting dose of S. aureus > 100,000-fold [27]. Biofilms are resistant to high levels of many antimicrobial agents [28,29], increasing the difficulty and cost of successful treatment. Once established, biofilm infections require removal of the prosthesis to achieve a cure [26]. Accurate diagnosis of PJIs usually requires a combination of preoperative and intraoperative tests, and standard treatment in the United States is a two-stage prosthetic exchange, separated by 6 weeks of intravenous (IV) antibiotic therapy acting on adhering stationary-phase microorganisms. The two-stage reimplantation technique involves removal of the prosthesis and resection of all infected tissue [30].

Guidelines for the management of PJIs have not yet been published, although the Infectious Diseases Society of America (IDSA) is preparing new guidelines for publication in 2008. In clinical practice, patients with PJIs involving MRSA isolates are often treated with a glycopeptide antibiotic such as vancomycin, which has been the standard therapy for MRSA infections for many years in the United States. However, the continued utility of vancomycin for MRSA infections, despite its sustained in vitro microbiologic inhibitory activity, is being questioned [31]. The detection of reduced susceptibility to vancomycin by routine susceptibility testing is unreliable, and vancomycin non-susceptibility is probably underreported [32]. While high-level resistance remains rare, an evolutionary change in S. aureus, evidenced by reduced susceptibility to vancomycin, is occurring [32,33]. Heteroresistance to vancomycin, as well as poor tissue penetration after its systemic administration [33], pose obstacles to successful therapy of MRSA infections with this glycopeptide. Additionally, patients previously exposed to vancomycin, as those with PJIs often are, appear to be at higher risk of infection by vancomycin-intermediate S. aureus (VISA), heterogeneous VISA (hVISA), and vancomycin-resistant S. aureus (VRSA) [32]. Treatment options for infections due to MRSA and with reduced susceptibility to vancomycin are limited.

The cyclic lipopeptide antibacterial agent daptomycin is the most recently introduced alternative to vancomycin for the treatment of MRSA infections. Clinical studies have demonstrated that daptomycin is as effective as standard therapies for cSSSI [34], diabetic foot infections [35], and complicated urinary tract infections [36]. Preclinical models of infection have suggested that daptomycin may have antibacterial activity in other types of infection, including osteomyelitis and foreign body infection due to S. aureus [37,38]. Here, we present prospective observational data collected from 30 patients treated with daptomycin for PJIs involving Gram-positive cocci.

MATERIALS AND METHODS

Thirty patients treated with daptomycin for a severe, Gram-positive PJI during a 12-month period were included in this prospective observational study. Data were collected with respect to age, sex, race, underlying illnesses, surgical procedures, culture site and pathogens, duration of daptomycin therapy, dosage, adverse effects, previous antibiotic use, and clinical outcomes. When possible, cultures were taken directly from the prosthetic device during surgery. Surgical interventions included removal of all hardware and repeated incision and debridement of the area until it was deemed clinically free from infection by the surgeon. Repeat cultures were obtained from some patients to determine if residual microbes were present. Clinical and microbiologic cure was defined as resolution or improvement of clinical infections, as demonstrated by negative microbiologic culture results, clinical signs, and magnetic resonance imaging (MRI) or computed tomography (CT) scans. Treatment failure was defined as recurrence of infection despite antibiotic therapy and appropriate surgical procedures and/or debridement. Laboratory testing included serum creatinine phosphokinase (CPK) levels (at admission and discharge), whole blood counts, alanine aminotransaminase, and aspartate aminotransferase. Routine follow-up evaluations were undertaken 2–4 weeks after the surgical intervention. Later follow-up assessments were performed, in some cases up to 12 months after a patient had received daptomycin therapy.

RESULTS

The mean age of daptomycin-treated patients was 67.3 years (range, 41–88 years) (Table 1). Seventeen patients (57%) were male, and 16 patients (53%) had an underlying diagnosis of diabetes mellitus. Twenty-three of the 30 patients (77%) had infections involving MRSA isolates, 4 (13%) had methicillin-sensitive S. aureus (MSSA) infections, 2 (7%) had MRSE infections, and 1 (3%) was culture negative. Twenty patients (67%) had MRSA pathogens with MICs to daptomycin < 0.5 ?g/mL. Eighty percent of patients (n = 24) underwent surgery before or upon starting treatment with daptomycin; the most common procedure was removal of hardware and debridement,

followed by incision and drainage. Some patients required both procedures, and 1 patient required amputation (Table 2). Seven patients had their prostheses removed before failing prior therapy. All patients who had an exchange arthroplasty has an antibiotic-impregnated spacer placed. Twenty-six (87%) of the 30 patients received daptomycin as second- or third-line therapy, after failing prior antibiotic therapy. Of these patients, 5 had at least 1 course of vancomycin monotherapy, and 7 others received vancomycin in combination with another agent. The mean duration of all prior therapy was approximately 30 days. The mean duration of daptomycin therapy was 37 days (range, 10–42 days), and most patients (73%) received IV daptomycin at a dosage of 6 mg/kg/day (Table 3). Three patients with reduced renal capacity at baseline (glomerular filtration rate < 30 mL/min/1.73 m2) were dosed at 4 mg/kg IV every 48 hours. Patients receiving hemodialysis received antibiotic treatment immediately after dialysis. To monitor patients' clinical responses and possible relapses, follow-up cultures were obtained from all patients with PJIs who underwent reimplantation.

At 12-month follow-up, daptomycin therapy was successful in 67% (20/30) of the patients who received it (Table 3). A cure rate of 66% was achieved in 13 patients with total knee arthroplasty infections; 13 patients (61%) with total hip arthroplasty infections were cured. The cure rate among 3 patients with total elbow arthroplasty infections was 66%; 1 patient with a total shoulder arthroplasty infection was cured. Of patients who were deemed cured after daptomycin therapy, none to date have experienced a recurrent or relapsing infection. One patient with diabetes experienced myalgia during daptomycin therapy and had a transient elevation in serum CPK levels after 14 days of therapy, which resulted in discontinuation of treatment. Of the 10 patients who failed daptomycin therapy, all had MRSA infection, and 9 had received previous antimicrobial therapy (vancomycin, n = 3; cephalosporin, n = 3; linezolid, n = 2; trimethoprim-sulfamethoxazole, n = 1). Three of the 10 patients (30%) who failed daptomycin therapy had not had their prostheses surgically removed.

DISCUSSION

To date, there have been no published studies of bone concentration and penetration of daptomycin in patients with or without infection, and no study has assessed the safety profile of daptomycin beyond 42 days. In the current study, IV daptomycin in combination with appropriate surgical interventions was effective in 66% of the patients who received it. While the recommended dose for daptomycin in the treatment of cSSSI is 4 mg/kg/day [18], 73% of patients in this study were dosed at 6 mg/kg/day (i.e., the approved dosage for treatment of S. aureus bacteremia and right-sided endocarditis), with a high degree of safety. Three of 8 patients (37%) receiving 4 mg/kg/day experienced successful outcomes, as did 17 of 22 patients (77%) who received 6 mg/kg/day. Our experience with other drugs used to treat bone and joint infections was the basis for determining the duration of daptomycin therapy in this study, which was approximately 6 weeks (actual mean duration of therapy, 37 days). Treatment failures that occurred before the administration of daptomycin therapy in this study included patients treated with appropriate antibiotics such as vancomycin or linezolid for an average of 30 days (range, 3–8 weeks). This has been the generally accepted standard of care for orthopedic-related infections caused by resistant Gram-positive organisms, and vancomycin with and without rifampin has also been used by the authors with variable success.

There are few other randomized, controlled clinical studies of antimicrobial treatment for patients with PJIs, despite the increasing prevalence of this type of infection in an aging population. Rifampicin has been shown to have excellent activity on slow-growing and implant-adherent staphylococci [39,40], and is frequently combined with a quinolone to prevent emergent staphylococcal resistance. The combination of rifampin and ciprofloxacin has been shown to be superior to rifampin alone for the treatment of orthopedic implant-related staphylococcal infections [41]. Controlled clinical trials of newer quinolones in the treatment of PJIs have not been completed.

Because of its oral bioavailability and activity against MRSA and VRE, the oxazolidinone linezolid is a possible alternative treatment for PJIs [42]. A European study of linezolid for the treatment of Gram-positive prosthetic hip and knee infections, including MRSA, resulted in 16 of 20 (80%) not needing further surgical substitution of prosthesis or surgical joint revision; 4 patients (20%) had relapsing infections [43]. A more recent study of linezolid in 51 patients with orthopedic infections (23 with PJIs) resulted in clinical and microbiologic failure in only 1 patient (2%). Seventeen infections (33%) required long-term suppression after remission, most often because of retained hardware. One patient developed reversible optic and irreversible

peripheral neuropathy after 24 months of treatment with linezolid [42].

The 67% overall treatment success rate of daptomycin found in this trial should be viewed in the context of current rates of successful treatment of MRSA PJIs. A 2007 retrospective prognostic study determined the effect of methicillin resistance on the outcome of patients with PJIs caused by S. aureus [44]. From January 1995 to December 2004, 33% of 137 episodes of PJI were the result of S. aureus (in monomicrobial or polymicrobial cultures). Thirty-three (24%) episodes among 31 patients were the result of methicillin-susceptible S. aureus, and 12 (9%) episodes among 12 patients were the result of MRSA. The overall treatment success rate was 62%. MRSA in periprosthetic tissue culture resulted in a higher risk of treatment failure (hazard ratio [H.R.] 9.2; 95% confidence interval [C.I.] 2.40–35.46) than methicillin-susceptible S. aureus when controlling for joint location (total knee arthroplasty vs. total hip arthroplasty [H.R. 5.8; 95% C.I. 1.52–22.19]) and removal of hardware (H.R. 0.24; 95% CI 0.077–0.75) [44]. Factors that may have prevented successful treatment with daptomycin in this study include possible biofilm formation on prostheses, delayed or non-removal of hardware, and subtherapeutic dosing of daptomycin (i.e., 4 mg/kg q24 or 48 h) in 8 patients. The 77% success rate among patients who received daptomycin 6 mg/kg/d compared with the 38% success rate among patients treated with 4 mg/kg/q24 or 48h supports use of a higher dosage in patients with difficult-to-treat MRSA infection of their prostheses. The absence of a comparative treatment arm and possible selection bias must be taken into account. Additionally, because patients studied also underwent a variety of concomitant surgical interventions, determining the precise role that daptomycin played in the successful outcomes is difficult. Failure of vancomycin, the gold standard for treating complicated bone and joint infections and PJIs, has been documented [45,46]. The ease of the daptomycin dosing regimen, its tolerability, and its lack of side effects make it a potential alternative to vancomycin or linezolid, as demonstrated in this trial by the successful outcomes of patients treated with daptomycin after vancomycin or linezolid treatment failure (n = 10). While larger, prospective clinical trials in patients with osteomyelitis and PJIs are necessary to confirm our findings, daptomycin was effective for the treatment of complicated PJIs involving MRSA and MSSA in the patient population studied.

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