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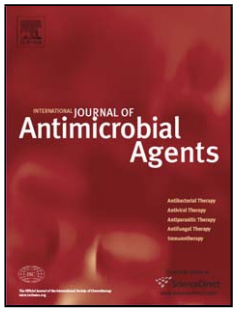

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High-dose daptomycin in documented *Staphylococcus aureus* infections

Matteo Bassetti [a,*], Elena Nicco [a], Francesca Ginocchio [a], Filippo Ansaldi [b], Daniela de Florentiis [b], Claudio Viscoli [a]

[a] *Infectious Diseases Division, San Martino Hospital and University of Genoa School of Medicine, Genoa, Italy*

[b] *Hygiene Unit, San Martino Hospital and University of Genoa School of Medicine, Genoa, Italy*

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* Corresponding author. Present address: Clinica Malattie Infettive, A.O.U. San Martino, Largo R. Benzi 10, 16132 Genova, Italy. Tel.: +39 010 555 5132; fax: +39 010 353 7680.

E-mail address: matteo.bassetti@hsanmartino.it (M. Bassetti).

ABSTRACT

Daptomycin is approved at a dose of 4–6 mg/kg/day for the treatment of complicated skin and soft-tissue infection and *Staphylococcus aureus* bloodstream infection. Clinical experience with doses >6 mg/kg/day is limited, but data reported to date suggest that daptomycin can be safe and effective at higher doses. We describe our experience with daptomycin at doses >6 mg/kg/day and ≤6 mg/kg/day for *S. aureus* infections. A retrospective chart review of all patients treated with daptomycin from January 2008 to 28 February 2010 was performed. During the study period, 53 patients received daptomycin, including 22 patients receiving daptomycin at a standard dose (SD) (mean 5 mg/kg/day, range 4–6 mg/kg/day) and 31 patients receiving a higher dose (HD) (mean 8 mg/kg/day, range 7–9 mg/kg). The median treatment duration was 13.5 days and 19 days for the SD and HD groups, respectively. Clinical success was observed in 16/22 patients (73%) in the SD group and 29/31 patients (94%) in the HD group ($P = 0.05$). Microbiological success was observed in 13/19 patients (68%) and 27/29 patients (93%) in the SD and HD groups, respectively ($P < 0.05$). Of the 53 patients, 2/22 treated with SD daptomycin and 3/31 treated with HD daptomycin experienced a grade 1 adverse event while receiving therapy (i.e. anaemia, diarrhoea, nausea, hypokalaemia and arthralgia) but did not require discontinuation of daptomycin treatment. These results suggest that daptomycin may be used at doses higher than 6 mg/kg/day without toxicity and possibly with better outcome than conventional doses. We recommend further randomised controlled prospective studies with higher doses of daptomycin.

1. Introduction

Daptomycin is a cyclic lipopeptide antibiotic with a unique mechanism of action against Gram-positive bacteria that provides potent and rapid bactericidal activity [1]. This bactericidal activity is concentration-dependent and its optimal expression may sometimes require levels equivalent to eight times the lipopeptide minimum inhibitory concentration (MIC) for a given strain [2]. Daptomycin is approved at a dose of 4 mg/kg for the treatment of complicated skin and soft-tissue infection (cSSTI) and at a dose of 6 mg/kg for *Staphylococcus aureus* bloodstream infection (BSI), including treatment of right-sided endocarditis. Although prospective randomised clinical studies have claimed that these dosage regimens are safe and effective for their respective indications [3,4], optimal doses level have not been firmly established. In recent years, reports of clinical failures and the emergence of resistant strains following daptomycin treatment have raised great concern [5,6]. As a result, higher doses of daptomycin are being proposed as an alternative for some difficult-to-treat infections such as complicated bacteraemia and endocarditis. Recently, doses of 10 mg/kg/day were studied using an in vitro model of staphylococcal endocarditis, with promising results in terms of efficacy and prevention of resistance [7].

Pharmacokinetic data from healthy volunteers indicate that daptomycin, dosed once daily at 12 mg/kg, achieved trough levels of ca. 20 μg/mL, suggesting that this regimen might have sufficient activity against organisms with higher MICs [8]. Clinical experiences with doses >6 mg/kg are limited, but data reported to date suggest that daptomycin appears to be safe and well tolerated even at higher doses [9–13]. A recent study of experimental foreign-body meticillin-resistant *S. aureus* infection suggested that high-dose daptomycin (10 mg/kg/day) ensured a profile of safety from

the development of resistance [14]. In this article, we describe our experience with the clinical use of daptomycin at doses >6 mg/kg/day and ≤6 mg/kg/day for documented *S. aureus* infections.

2. Methods

A retrospective chart review of patients treated with daptomycin for a minimum of 10 days at San Martino University Hospital (Genoa, Italy) from January 2008 to 28 February 2010 was conducted. The review was approved by the local institutional review board; patient consent was not required because of the observational nature of the study. Patients included in the analysis were divided in two groups, those who received daptomycin at doses >6 mg/kg/day and those receiving ≤6 mg/kg/day in documented *S. aureus* infections. Clinical data were collected from medical records and included age, sex, co-morbid conditions, clinical diagnosis, microbiological isolate identification and antibiotic susceptibility, dose and duration of daptomycin treatment, adverse clinical events and creatine phosphokinase (CPK) levels. Susceptibilities of the isolates to daptomycin and vancomycin were determined by Etest (AB BIODISK, Solna, Sweden). Safety was determined using any adverse events documented in the medical record. Adverse events were graded 1–4 [15]. CPK levels were monitored after 7, 14 and >14 days in the two groups. Significant elevation in CPK level was defined as an increase in serum CPK value 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. Infections were classified as uncomplicated BSI, complicated BSI, infective endocarditis, cSSTI and osteomyelitis. Definitions of uncomplicated BSI, complicated BSI and infective endocarditis were consistent with those used in published studies

[3]. To assess the patient's overall clinical and microbiological response, the following categories were used: clinical success, defined as complete resolution of all signs and symptoms of infection; microbiological success, defined as eradication or presumed eradication of all baseline infecting pathogens and no isolation of superinfecting pathogens post therapy; clinical failure, defined as either no improvement or the need for other antibiotics to be added or substituted before improvement occurred; and microbiological failure, defined as the presence of a persisting pathogen or a superinfecting pathogen post therapy.

Comparisons of qualitative demographic, clinical and microbiological data as well as clinical and microbiological response rates between standard dose (SD) and higher dose (HD) groups were analysed by Fisher's exact test. Age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, duration of hospitalisation and duration of therapy between SD and HD groups as well as CPK levels between different times and between the two treatment groups were compared by Wilcoxon and Kruskal–Wallis tests.

3. Results

During the study period, 53 patients received daptomycin for *S. aureus* infections, including 22 patients in the SD group receiving a mean of 5 mg/kg/day (range 4–6 mg/kg/day) and 31 patients in the HD group receiving a mean of 8 mg/kg/day (range 7–9 mg/kg). The characteristics of the patients are summarised in Table 1.

The two groups were comparable in terms of age, gender, underlying conditions, types of infection and type of *S. aureus.* Duration of hospitalisation [median 15 days

(10–90th percentile 8.3–54.4 days) vs. 23 days (11–32 days)], APACHE II score [median 12 (10–90th percentile 7.3–22.4) vs. 16 (9–21.8)] and duration of therapy (median 13.5 days (10–90th percentile 10–51.3 days) vs. 19 days (14–52.2 days)] were higher in the HD group.

All of the *S. aureus* isolates were susceptible to daptomycin [MIC for 90% of the organisms (MIC_{90}) = 0.5 μg/mL, MIC range ≤0.06–1 μg/mL). All patients included in the analysis received a minimum of 10 days of daptomycin treatment with a median of 16 days of treatment (range 10–92 days). All 53 patients underwent CPK analysis during treatment (maximum every 3 days). Clinical success was observed in 16/22 patients (73%) in the SD group and 29/31 patients (94%) in the HD group ($P = 0.05$). Microbiological success was observed in 13/19 patients (68%) and 27/29 patients (93%) in the SD and HD groups, respectively ($P < 0.05$) (Table 2).

Of the 53 patients analysed, 2/22 (9%) treated with SD and 3/31 (9.7%) treated with HD experienced grade 1 adverse events while receiving therapy (i.e. anaemia, diarrhoea, nausea, hypokalaemia and arthralgia) but did not require discontinuation of daptomycin treatment. Differences in CPK levels were not observed either between different times or between the two treatment groups (Fig. 1). Only one patient (3.2%) treated with HD experienced significant grade 3 CPK level elevation (levels >1000 U/L); daptomycin treatment was discontinued and CPK levels returned to normal within 1 week.

4. Discussion

The appearance of clinical failures and resistant strains during daptomycin treatment has led to the suggestion that daptomycin might be used at higher doses for difficult-to-treat infections [5,6]. In San Martino University Hospital, many physicians have started to use daptomycin at doses higher than recommended owing to this suggestion. The results of this experience suggest that daptomycin can be used at doses >6 mg/kg/day without significant toxicity and possibly with better outcome than conventional doses.

The clinical and microbiological success rates observed in this study with higher doses (mean dose 8 mg/kg/day) were superior to those observed with standard doses (mean dose of 5 mg/kg/day) and this observation may represent the rationale for planning randomised clinical trials comparing standard versus higher doses.

To date there are limited clinical data for the use of daptomycin at doses >6 mg/kg [9–13]. In particular, there are no studies comparing the clinical and microbiological efficacies of higher doses with standard doses. In general, daptomycin is well tolerated, with few significant adverse events other than CPK level elevation. Clinical studies to date report an incidence of significant CPK level elevation of 2.1% with a dosage of 4 mg/kg in cSSTI and 8.3% with 6 mg/kg for up to 6 weeks in patients with *S. aureus* bacteraemia or endocarditis [3,4]. Two recent studies used higher doses (≥8 mg/kg) of daptomycin for a variety of Gram-positive infections [12,13]. CPK level elevations occurred in 6–9% of patients treated with daptomycin, and discontinuation due to grade 3 adverse events occurred in 2.1% and 4.9%, respectively [12,13]. A recent report of a pilot study on the treatment of cSSTI that used higher doses of

daptomycin (10 mg/kg/day for 4 days) demonstrated an overall incidence of CPK level elevation of 8.3% [11]. The incidence of significant CPK elevations observed in this study (3.2%) is similar to or lower than that reported by other authors using standard doses [3,4,11–13].

There are several limitations to this study, including lack of randomisation, the small cohort of patients, its retrospective nature, variable types of infection and the longer duration of treatment in the HD group.

Our experience suggests that higher doses of daptomycin are safe and might be more effective than standard doses in *S. aureus* infections. This observation might represent the rationale for planning and conducting randomised clinical trials of higher versus standard dosing.

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None.

Competing interests

MB has been a consultant to Novartis and a member of the speakers' bureau for Novartis. All other authors declare no competing interests.

Ethical approval

The review was approved by the Comitato Etico dell Azienda Ospedaliera Universitaria San Martino di Genova on October 2007; patient consent was not required because of the observational nature of the study.

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Fig. 1. Creatine phosphokinase (CPK) levels observed in the standard dose (SD) and higher dose (HD) daptomycin groups at different times. The lower and higher edges of the boxes correspond to the 25th and 75th percentiles, respectively; the bars from the sides of the box extend to the 10th and 90th percentiles.

Table 1

Characteristics, types of infection, type of *Staphylococcus aureus* and duration of therapy for study patients in the daptomycin standard dose (SD) and higher dose (HD) groups

Characteristic	SD group (*N* = 22)	HD group (*N* = 31)	*P*-value
Age (years) [median (10–90th percentile)]	64.5 (49.8–79)	68 (39.4–80.8)	N/S
Gender male [*n* (%)]	14 (64)	24 (77)	N/S
Duration of hospitalisation (days) [median (10–90th percentile)]	15 (8.3–54.4)	23 (11–32)	<0.01
APACHE II score [median (10–90th percentile)]	12 (7.3–22.4)	16 (9–21.8)	0.03
Underlying conditions [*n* (%)]			
Diabetes mellitus	3 (14)	5 (16)	N/S
Peripheral vascular disease	3 (14)	6 (19)	N/S
Immunocompromised	2 (9.1)	5 (16)	N/S
Neutropenia	1 (4.5)	3 (10)	N/S
Type of infection [*n* (%)]			
Uncomplicated BSI	10 (45)	7 (23)	N/S
Complicated BSI	3 (14)	8 (26)	N/S
cSSTI	3 (14)	5 (16)	N/S
Left-sided endocarditis	2 (9.1)	4 (13)	N/S
Right-sided endocarditis	2 (9.1)	5 (16)	N/S
Osteomyelitis	2 (9.1)	2 (6.5)	N/S
Type of *S. aureus* [*n* (%)]			
MRSA	19 (86)	27 (87)	
MSSA	3 (14)	4 (13)	N/S
Duration of therapy (days) [median (10–90th percentile)]	13.5 (10–51.3)	19 (14–52.2)	0.02

N/S, not significant ($P \geq 0.05$); APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; cSSTI, complicated skin and soft-tissue infection; MRSA, meticillin-resistant *S. aureus* MSSA, meticillin-sensitive *S. aureus*.

Table 2

Clinical and microbiological outcomes of higher dose (HD) and standard dose (SD) daptomycin

	Daptomycin SD	Daptomycin HD	*P*-value
Clinical success [*n*/*N* (%)]	16/22 (73)	29/31 (94)	0.05
Uncomplicated BSI	9/10	7/7	N/S
Complicated BSI	2/3	7/8	N/S
cSSTI	2/3	5/5	N/S
Left-sided endocarditis	1/2	¾	N/S
Right-sided endocarditis	1/2	5/5	N/S
Osteomyelitis	1/2	2/2	N/S
Microbiological success [*n*/*N* (%)]	13/19 (68)	27/29 (93)	<0.05
Uncomplicated BSI	6/8	5/5	N/S
Complicated BSI	2/3	7/8	N/S
cSSTI	2/2	5/5	N/S
Left-sided endocarditis	1/2	3/4	N/S
Right-sided endocarditis	1/2	5/5	N/S
Osteomyelitis	1/2	2/2	N/S

BSI, bloodstream infection; N/S, not significant ($P \geq 0.05$); cSSTI, complicated skin and soft-tissue infection.

Edited Figure 1