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Safety of daptomycin in patients completing more than 14 days of therapy: results from the Cubicin® Outcomes Registry and Experience☆

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ABSTRACT

Patients with complicated infections may receive daptomycin for extended periods. This retrospective analysis was conducted to describe the safety profile of daptomycin in patients completing >14 days of therapy. In the Cubicin® Outcomes Registry and Experience (CORE®) 2005–2009, a retrospective, multicentre, observational registry, patients completing >14 days of daptomycin were studied. Investigators assessed adverse events (AEs) using ICH-E2A definitions of seriousness/severity ≤30 days after completing daptomycin. AEs were grouped by onset at ≤14, 15–28 and >28 days after starting daptomycin. In total, 2263 patients received >14 days of daptomycin. The most common indications were complicated skin and skin-structure infection (25.5%) and osteomyelitis (21.7%). Regarding AEs, 205 patients (9.1%) experienced AEs with an onset ≤14 days of therapy, 168 (7.4%) between 15–28 days and 108 (4.8%) >28 days; a total of 389/2263 patients experienced 814 AEs. The most common AE was increased blood creatine phosphokinase (CPK), occurring in 49 patients (2.2%) during ≤14 days of therapy, 32 (1.4%) between 15–28 days and 10 (0.4%) >28 days. In 183/2263 patients (8.1%), 264 AEs were possibly related to daptomycin. Serious AEs occurred in 153/2263 patients (6.8%). Eighty-nine (3.9%) of 2263 patients had daptomycin discontinued due to AEs, with 36 discontinued due to increased CPK. The overall mortality rate was 63/2263 (2.8%); 4 patients died of a possibly related AE. The most common AEs with onset <14 days were similar to those occurring between 15–28 days and >28 days. Daptomycin appears to be safe in patients treated for >14 days.

1. Introduction

Complicated *Staphylococcus aureus* infections may require an extended duration of treatment with antimicrobial therapy. A minimum of 2 weeks of therapy is recommended for patients with uncomplicated bacteraemia caused by meticillin-resistant *S. aureus* (MRSA); in patients with complicated bacteraemia and endocarditis, 2–4 weeks and 6 weeks, respectively, are recommended [1].

Daptomycin has been shown to be safe and effective with a treatment duration up to 14 days in patients with complicated skin and skin-structure infections (cSSSIs) [2]. In addition, daptomycin was shown to be safe and effective in patients with *S. aureus* bacteraemia receiving 2–6 weeks of therapy, including those with infective endocarditis; however, the median duration of therapy was only 14 days [3]. There have been case and registry reports of the safety and efficacy of prolonged use of daptomycin for complicated infections; however, information on the safety of daptomycin for prolonged use is limited [4–6]. The purpose of this study was therefore to assess the safety of daptomycin in patients who completed >14 days of therapy.

2. Patients, materials and methods

Patients enrolled in the Cubicin® Outcomes Registry and Experience (CORE®) study and who completed >14 days of daptomycin therapy between 1 January 2005 and 31 December 2009 were eligible for this analysis. CORE is a multicentre, retrospective registry of patients in the USA who received daptomycin and includes a total of 5482 patients. Institutional review board approval was obtained from all sites prior to the registry. Sequential patients who were treated with one or more doses of daptomycin and who were not receiving daptomycin as part of a clinical trial were included in the registry. Clinical information was collected on a standardised case report form from medical records by trained study investigators and included age ranges and other demographic characteristics, underlying diseases, daptomycin dosage, length of therapy, and the setting in which therapy was administered (acute, subacute or outpatient). The methods for CORE have been published previously [7,8].

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Table 1
Selected demographic and baseline characteristics of the safety population.[a]

Characteristic	*n* (%)		
	Patients with no AEs (*N* = 1874)	Patients with AEs (*N* = 389)	Total (*N* = 2263)
Sex			
Female	872 (46.5)	192 (49.4)	1064 (47.0)
Male	1002 (53.5)	197 (50.6)	1199 (53.0)
Weight (kg)			
Median	82.6	83.6	82.7
Range	33.6–272.0	37–205	33.6–272.0
Age group			
<18 years	13 (0.7)	2 (0.5)	15 (0.7)
18–30 years	106 (5.7)	23 (5.9)	129 (5.7)
31–50 years	546 (29.1)	95 (24.4)	641 (28.3)
51–65 years	628 (33.5)	137 (35.2)	765 (33.8)
66–80 years	465 (24.8)	111 (28.5)	576 (25.5)
≥81 years	116 (6.2)	21 (5.4)	137 (6.1)
Race[b]			
Asian	13 (1.4)	1 (0.4)	14 (1.2)
Black or African–American	109 (11.8)	46 (19.9)	155 (13.4)
White	658 (71.2)	156 (67.5)	814 (70.5)
Native Hawaiian or other Pacific Islander	1 (0.1)	2 (0.9)	3 (0.3)
American Indian or Alaska Native	5 (0.5)	1 (0.4)	6 (0.5)
Other	52 (5.6)	5 (2.2)	57 (4.9)
Unknown	86 (9.3)	20 (8.7)	106 (9.2)
CL_{Cr}			
Unknown initial estimate	187 (10.0)	21 (5.4)	208 (9.2)
<30 mL/min	268 (14.3)	77 (19.8)	345 (15.2)
≥30 mL/min	1419 (75.7)	291 (74.8)	1710 (75.6)
CL_{Cr} subset from 2007 to 2009[c]			
<30 mL/min[c]	90 (9.7)	29 (12.6)	119 (10.3)
30 to <50 mL/min[c]	126 (13.6)	30 (13.0)	156 (13.5)
50–80 mL/min[c]	186 (20.1)	50 (21.6)	236 (20.4)
>80 mL/min[c]	443 (47.9)	108 (46.8)	551 (47.7)
Unknown[c]	79 (8.5)	14 (6.1)	93 (8.1)
Initial dose (mg/kg)			
Median	6.00	6.00	6.00
Range	1.0–14.5	2.8–13.5	1.0–14.5
Setting			
Inpatient/outpatient	1251 (66.8)	286 (73.5)	1537 (67.9)
Inpatient only	47 (2.5)	13 (3.3)	60 (2.7)
Outpatient only	576 (30.7)	90 (23.1)	666 (29.4)
Infection type			
cSSSI	502 (26.8)	74 (19.0)	576 (25.5)
Osteomyelitis	404 (21.6)	87 (22.4)	491 (21.7)
Bacteraemia	355 (18.9)	99 (25.4)	454 (20.1)
uSSSI	183 (9.8)	35 (9.0)	218 (9.6)
Endocarditis	109 (5.8)	27 (6.9)	136 (6.0)
Other	321 (17.1)	67 (17.2)	388 (17.1)

AE, adverse event; CL_{Cr}, creatinine clearance; cSSSI, complicated skin and skin-structure infection; uSSSI, uncomplicated skin and skin-structure infection.
[a] Data are *n* (%) unless otherwise stated.
[b] Data only available from 2007 to 2009 (*N* = 924 patients with no AEs; *N* = 231 patients with AEs; total *N* = 1155); percentage based on those years.
[c] CL_{Cr} in expanded intervals available from 2007 to 2009 (*N* = 924 patients with no AEs; *N* = 231 patients with AEs; total *N* = 1155); percentage based on those years.

Adverse events (AEs) were stratified as those occurring within ≤14 days, 15–28 days and >28 days after starting daptomycin therapy. This methodology precluded an examination of AEs in patients discontinuing daptomycin prior to completing >14 days of treatment. Therefore, if an AE occurred in the 14 days when the patient was on daptomycin therapy, but the patient discontinued therapy after 14 days of receiving daptomycin, these events are described in the paper. Throughout the daptomycin treatment period and 30 days following the last dose, changes in physical findings, clinical signs and symptoms, and laboratory values consistent with AEs were collected. In addition, the day of AE onset relative to daptomycin start, the relationship to daptomycin (not related or possibly related), whether daptomycin was discontinued due to an AE, and patient death (if applicable) were documented.

If a patient had the same AE across different onset strata, the patient was categorised in both strata; however, if a patient had two AEs within one time period, that patient was counted once for that AE in that duration stratification. All AEs where the onset day was unknown were excluded from the stratified analysis. Patients who had an AE that occurred after Day 14 but received <14 days of daptomycin therapy were excluded from this analysis.

Investigator descriptions of AEs and serious AEs (SAEs) were standardised using the '*Medical dictionary for regulatory activities*' (MedDRA). The AE was considered serious if it exhibited or led to any of the following characteristics: death; life-threatening; disability/incapacity; hospitalisation; congenital anomaly/birth defect; or an important medical event.

3. Results

Two patients with three AEs (renal failure in one patient, and sepsis and liver failure in another patient) were excluded from the analysis since the onset was unknown. A total of 2263 patients received daptomycin for >14 days and the baseline characteristics are summarised in Table 1. There were no noteworthy differences between patients experiencing AEs and those not having an AE. A similar number of patients received daptomycin for 15–28 days (1076; 47.5%) or >28 days (1187; 52.5%).