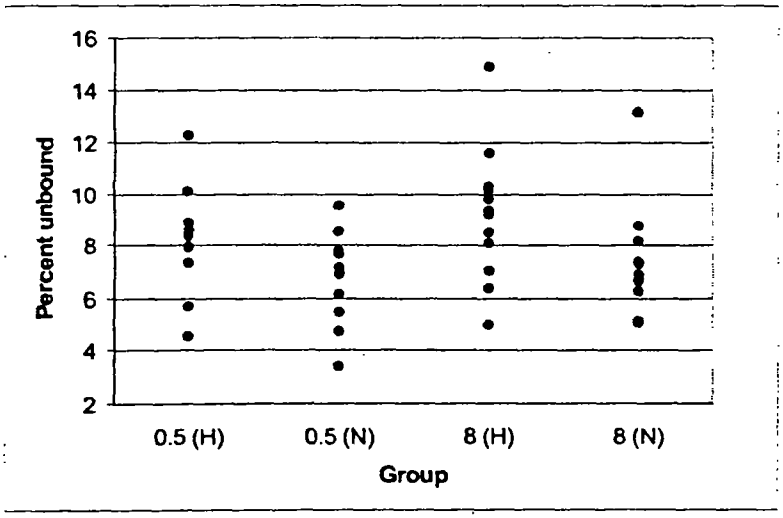
Table 4. Geometric mean ratios (hepatic impairment/normal hepatic function) and 90% confidence intervals for subjects with hepatic impairment and normal hepatic function

	Total		Unbound	
Parameter	Point estimate	90% CI	Point estimate	90% CI
AUC_{0-24}	0.926	(0.830 to 1.035)	1.112	(0.918 to 1.347)
$AUC_{0-\infty}$	0.922	(0.803 to 1.058)	1.106	(0.917 to 1.336)
C_{max}	0.959	(0.856 to 1.074)	1.150	(0.927 to 1.428)
CL_T	1.071	(0.925 to 1.239)	0.876	(0.723 to 1.063)
CL_R	1.261	(0.970 to 1.639)	1.061	(0.791 to 1.422)
Ae_{24}	1.198	(0.930 to 1.543)	---	---

The 90% confidence intervals of the geometric mean ratios for $AUC_{0-\infty}$, C_{max}, and CL_T were within 0.80 to 1.25 range based on total daptomycin concentrations but outside of the 0.80 to 1.25 range based on unbound daptomycin concentrations. The differences in the pharmacokinetic parameter estimates based on unbound concentrations were not statistically significantly different between subjects with impaired hepatic function and normal hepatic function. Thus, the magnitude of the difference of the $AUC_{0-\infty}$ and C_{max} between subjects with hepatic impairment and healthy subjects does not warrant a dosage adjustment.

The mean percentage of unbound daptomycin at 0.5 hrs and 8 hrs in subjects with hepatic impairment were 8.13% and 9.20%, respectively. The mean percentage of unbound daptomycin at 0.5 hrs and 8 hrs in healthy subjects were 6.72% and 7.38%, respectively. At 0.5 hrs and 8 hrs, the percent unbound was 21.1% and 16.1% greater, respectively in subjects with hepatic impairment. A comparison of the percentage unbound of daptomycin is shown in figure 2.

Figure 2. Mean individual percent unbound of daptomycin at 0.5 hrs and 8 hrs in subjects with hepatic impairment (H) and normal hepatic function (N)



CONCLUSIONS:

The $AUC_{0-\infty}$ and C_{max} were not statistically significantly different between subjects with impaired hepatic function and normal hepatic function based on total and unbound daptomycin concentrations.

The fraction of unbound daptomycin increased 21.1% at the end of the infusion and 16.1% at 8 hrs after the start of the infusion in subjects with hepatic impairment compared to healthy subjects.

No dosage adjustment of daptomycin is recommended for subjects with hepatic impairment.

COMMENTS:

1. The sponsor has not provided data to support the stability of the daptomycin — ' assay for daptomycin in urine and the — assay for daptomycin in serum (— — and the stability of daptomycin in extracted plasma samples). The sponsor is encouraged to submit all validation data with the validation report.

A single dose study to evaluate the pharmacokinetics and safety of Cidecin® (daptomycin for injection) in healthy geriatric and younger healthy subjects following a dose of 4 mg/kg total body weight (Protocol DAP-GER-01-11)

Dates: January 7, 2002 to March 6, 2002
Clinical sites:

Analytical site:

RATIONALE:
The pharmacokinetic differences between the young and elderly are generally attributed to physiological and pathophysiological changes that occur more often in the elderly, which can include altered renal function. This study was undertaken to assess the single-dose pharmacokinetics and safety of daptomycin in healthy geriatric subjects compared with younger healthy subjects to determine if pharmacokinetic or safety differences exist between the two populations.

OBJECTIVES:
The primary objective of this study was to evaluate the pharmacokinetics (single dose) of daptomycin in healthy geriatric subjects ≥75 years of age and younger healthy subjects 18 to 30 years of age. The secondary objective was to evaluate the safety of daptomycin in healthy geriatric subjects and younger healthy subjects.

FORMULATIONS:
Daptomycin 500 mg vial (Cubist, Lot No. 680413A)

STUDY DESIGN:
This study was an open-label, single-dose, parallel design, two-center study to evaluate the pharmacokinetics of daptomycin in 12 healthy adult subjects ≥75 years old and 11 healthy young subjects between 18 and 30 years old. Planned enrollment called for 12 geriatric subjects and 12 younger subjects and an attempt was made to enroll an equal number of men and women in each group. All subjects received a single dose of intravenous (IV) daptomycin at 4 mg/kg based on total body weight in 50 mL of normal saline.

Blood samples for determination of daptomycin concentrations were obtained predose, mid-way through the infusion (0.25 hrs), end of the infusion (0.5 hrs), 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hrs from the initiation of the infusion.

Urine samples for determination of daptomycin concentrations were obtained at predose and then at 0-2 hrs, 2-4 hrs, 4-8 hrs, 8-12, 12-16 hrs, and 16 to 24 hrs from the initiation of infusion. Urine was collected for 24 hrs to allow a 24-hr urine creatinine clearance calculation.

DAPTOMYCIN ASSAY METHODOLOGY:

Criterion	Plasma	Urine	Comments
Concentration range	3.28 to 545 µg/mL	3.36 to 562 µg/mL	Satisfactory
LLOQ			Satisfactory
Linearity			Satisfactory
Accuracy			Satisfactory
Precision			Satisfactory
Specificity	Satisfactory	Satisfactory	Satisfactory
Stability	Not stated	Not stated	Unsatisfactory

DATA ANALYSIS:

Plasma daptomycin concentration data were analyzed by non-compartmental pharmacokinetic analysis. The following parameters were determined for plasma daptomycin concentration data: the maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), plasma concentration at 24 hrs post-dose (C_{24}), the area under the plasma concentration-time curve from zero to the last quantifiable concentration (AUC_{0-t}), AUC from zero to infinity ($AUC_{0-\infty}$), plasma clearance (CL_T), volume of distribution ($Vz = CL/Ke$), volume of distribution at steady state ($V_{SS} = CL \times MRT$), mean residence time (MRT), and terminal elimination half-life ($t_{1/2}$).

The following parameters were calculated based on daptomycin urine concentration data: the renal clearance (CL_R) and the fraction of dose excreted in urine as parent drug over 24 hrs (Ae).

STATISTICAL ANALYSIS:

Pharmacokinetic parameters were summarized as mean, SD, median, and range. The geometric mean ratios and 90% confidence intervals for daptomycin C_{max}, $AUC_{0-\infty}$, CL_T, CL_R, and Fe were reported.

RESULTS:

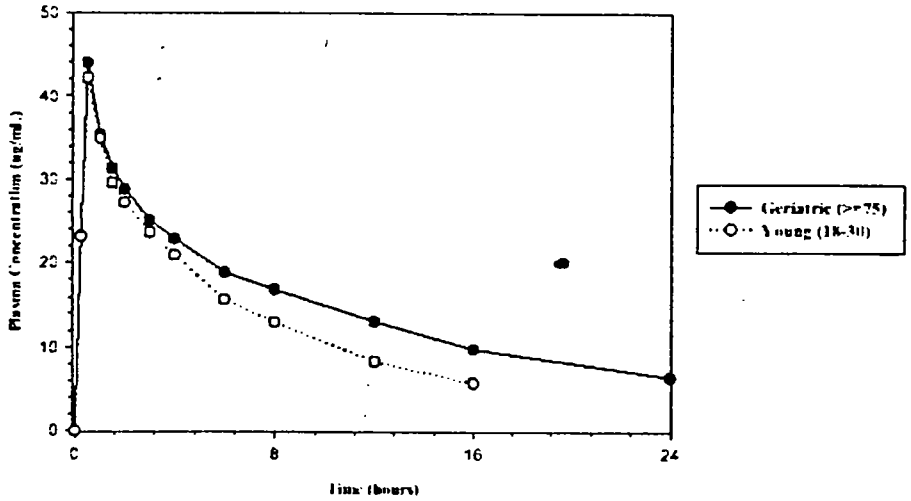
Although 12 healthy elderly and 12 healthy young subjects were enrolled into the study, only 11 healthy young subjects completed the study. Subject 021 was excluded from the pharmacokinetic analysis because this subject received a dose of daptomycin over 8 mg/kg, twice the protocol dose. The mean (SD) demographic data for the 23 subjects who completed the study are shown in Table 1. Most of the subjects were Hispanic (50% of elderly and 100% of young) and the elderly subjects tended to be taller, weight more, and have a lower creatinine clearance.

Table 1. Mean (SD (range) demographics for healthy elderly and healthy young subjects

Group	N	Age (yrs)	Weight (kg)	Height (cm)	Estimated CL_{CR} (mL/min)	Measured CL_{CR} (mL/min)
Healthy elderly	2F/10M	77.3 (2.5)	77.0 (8.2)	164.2 (5.9)	57.6 (12.6)	66.8 (15.1)
Healthy young	6F/5M	23.5 (4.3)	64.8 (10.2)	163.1 (6.7)	94.7 (14.5)	77.9 (17.2)

The mean plasma concentration-time profiles of daptomycin following a single dose of daptomycin IV 4 mg/kg in elderly and young subjects are shown in Figure 1. Although the mean plasma concentrations of daptomycin were similar immediately following administration, plasma concentration were greater in healthy elderly subjects compared to healthy young subjects and may be due to differences in clearance among the two groups of subjects.

Figure 1. Mean plasma concentration-time profiles of daptomycin following a single dose of 4 mg/kg IV to healthy elderly and young subjects



The daptomycin pharmacokinetic parameter estimates following the administration of a single dose of daptomycin IV 4 mg/kg are shown in Table 2. The mean C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 0.04-fold, 0.46-fold, and 0.58-fold greater, respectively in elderly subjects than young subjects. The sponsor's estimate of AUC_{0-24} may be an underestimate in young subjects since a plasma concentration of zero was used at 24 hrs (10 of 11 subjects) when the concentration was below the LLOQ. The mean CL_T, CL_R, and Ae were 0.35-fold, 0.41-fold, and 0.19-fold lower in elderly subjects compared to young subjects. The Vz and V_{ss} were 0.13-fold and 0.14-fold greater in elderly subjects. The terminal elimination half-life was 0.74-fold greater.

Table 2. Mean (CV%) daptomycin pharmacokinetic parameter estimates when administered to healthy elderly and healthy young subjects

Parameter	Healthy Elderly (n=12)	Healthy Young (n=11)
AUC_{0-t} (µg*hr/mL)	361 (18%)	248 (13%)
AUC_{0-24} (µg*hr/mL)	361 (18%)	268 (11%)
$AUC_{0-\infty}$ (µg*hr/mL)	474 (23%)	301 (12%)
C_{max} (µg/mL)	44.0 (17%)	42.3 (15%)
C_{24} (µg/mL)	6.4 (29%)	3.4[a]
T_{max} (hrs)	0.5 (7%)	0.5 (28%)
CL_T (mL/hr/kg)	9.86 (25%)	15.09 (16%)
CL_R (mL/hr/kg)	4.27 (40%)	7.20 (24%)
Vz (L/kg)	0.166 (29%)	0.147 (14%)
Vss (L/kg)	0.155 (27%)	0.136 (13%)
Half-life (hrs)	11.86 (19%)	6.80 (8%)
Ae (%)	34.3 (46%)	42.6 (16%)

a - n=1; the plasma concentration was below the LOQ [redacted] by 24 hrs in 10 of 11 healthy young subjects

The reviewer calculated the geometric mean ratios (healthy elderly/healthy young) and 90% confidence intervals for daptomycin C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, CL_T, CL_R and Ae (see Table 3). The AUC_{0-t}, $AUC_{0-\infty}$, CL_T, CL_R and Fe were statistically significantly different between healthy elderly and healthy young subjects. The 90% confidence intervals for daptomycin C_{max} was within the predetermined limits of 0.80 to 1.25 and was not statistically significantly different between the two groups of subjects.

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