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Pharmacokinetics and Safety of Daptomycin in Young Infants

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Abstract

Background: Daptomycin is approved for the treatment of complicated skin and skin structure infections, *Staphylococcus aureus* endocarditis, and bacteremia in adults. Clearance of daptomycin is higher in younger children (2-6 years of age) compared to adolescents and adults. Little data is available regarding the safety or pharmacokinetics (PK) of daptomycin in young infants. The primary objective of this study was to characterize daptomycin single-dose PK and safety in young infants.
Methods: Subjects <120 days of age with suspected systemic infections were eligible for the study. Each subject was given a single 6 mg/kg intravenous dose of daptomycin over 60 minutes. Plasma PK samples were collected 0.5-1, 2-4, 4-6, 12-18, and 20-24 hours from the end of the infusion. PK parameters were calculated by non-compartmental analysis using WinNonLin v.6 (Pharsight Corp., Cary, NC). Laboratory data pre and post infusion were compared using a Wilcoxon signed rank test. The relationship between clearance and postnatal and postmenstrual age was determined using linear regression.
Results: Data from 13 infants (55 plasma samples) are presented. Median gestational age at birth, birth weight, and postnatal age were 31 weeks [range; 23, 39], 1750 g [560, 3950], and 3 days [1, 85], respectively. Median plasma clearance, volume of distribution at steady state, and area under the curve at 24 hours were 0.020 L/hr/kg [0.016, 0.031], 0.20 L/kg [0.11, 0.27], and 276.9 mg·h/L [182.3, 340.2], respectively. Daptomycin clearance was not related to postnatal age or postmenstrual age, p=0.49 and p=0.77, respectively. The median measured maximal plasma concentration and time of maximal concentration were 27.2 mg/L [16.0, 33.3] and 0.5 hours [0.2, 2.3], respectively. No adverse events related to daptomycin were observed. No difference in plasma creatinine phosphokinase was observed before and after daptomycin dosing, 108 IU/L [47, 564] vs. 86 [36, 506], p=0.25.
Conclusions: Daptomycin clearance in young infants was similar to clearance in 2-6 year old children and higher than the clearance in adolescents and adult subjects. Single doses of 6 mg/kg of daptomycin were well tolerated in this small cohort of young infants.

Introduction

Gram-positive bacteria are the most common cause of late-onset sepsis in the neonatal intensive care unit.

Daptomycin is a cyclic lipopeptide antibiotic and is approved for *Staphylococcus aureus* bloodstream infections caused by methicillin-susceptible and methicillin resistant isolates.

Limited daptomycin pharmacokinetic (PK) data available in young infants suggest that drug disposition of daptomycin differs from adults.

Methods

Single center, PK and safety study of daptomycin in young infants.

Inclusion criteria: < 120 days of age; suspected systemic infection.

Exclusion criteria: serum creatinine >1.0 mg/dL; concomitant administration of tobramycin.

Each infant received a single 6 mg/kg intravenous dose of daptomycin over 60 min.

Samples collected 30 min-1 hr, 2-4 hr, 4-6 hr, 12-18 hr, and 20-24 hr from the end of infusion.

Liquid chromatography/mass spectrometry assay.

Noncompartmental methods; 24-hour area under the drug concentration curve (AUC_{24}) was calculated by the linear trapezoidal rule.

The relationship between clearance (CL) and covariates was determined using linear regression. Covariates analyzed: postnatal age, gestational age and, postmenstrual age.

Results

Table 1: Demographics

	N = 13 (55 samples)
Gestational age (weeks)	31 (23, 39)
Birth weight (g)	1750 (560, 3950)
Postnatal age (days)	3 (1, 85)
Dosing weight (g)	1780 (600, 3984)
Female gender (%)	8 (62)
Race	
White (%)	9 (69)
African American (%)	3 (23)
Other (%)	1 (8)
Hispanic ethnicity (%)	1 (8)

Data are median (range) unless otherwise stated

Table 2: PK Parameters

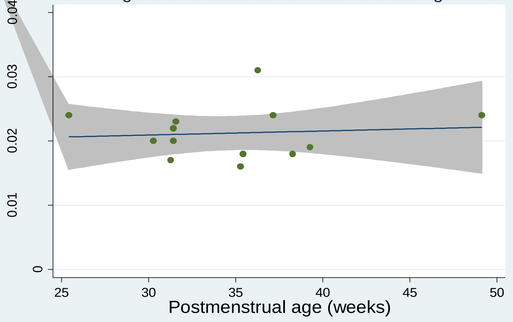
Postnatal age (days)	Gestational age (weeks)	V_{ss} (L/kg)	CL (L/hr/kg)	AUC_{24} (mg·h/L)	C_{max} (mg/L)	T_{max} (h)*
1	37	0.24	0.024	219.6	17.1	0.5
2	30	0.11	0.020	294.8	30.2	0.2
2	36	0.24	0.031	182.5	16.0	1.8
2	39	0.20	0.019	276.9	26.1	0.5
3	25	0.21	0.024	236.4	26.8	0.5
3	31	0.16	0.022	263.2	27.9	0.9
3	35	0.21	0.018	307.2	32.7	2.3
3	31	0.14	0.020	291.3	30.9	0.5
18	29	0.27	0.023	226.7	16.1	0.5
23	32	0.21	0.016	308.3	27.2	0.5
58	23	0.15	0.017	340.2	33.3	0.7
65	29	0.12	0.018	328.5	31.4	0.6
85	37	0.16	0.024	244.0	22.8	0.8
Median	**31**	**0.20**	**0.020**	**276.9**	**27.2**	**0.5**

*Times are relative to end of infusion

Table 3: Laboratory Values

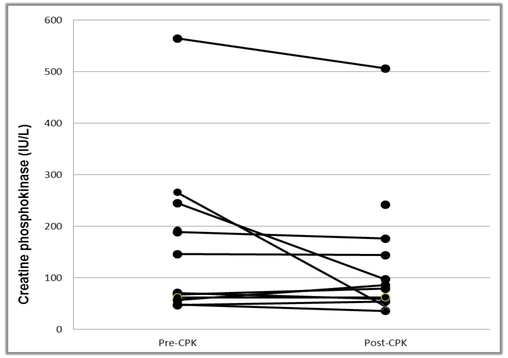
	Pre-dose	Post-dose	P
Serum Chemistry			
Sodium (mmol/L)	139 (133, 145)	140 (134, 143)	0.96
Potassium (mmol/L)	4.2 (3.6, 5.5)	4.6 (3.4, 6.0)	0.80
Calcium (mmol/L)	9.2 (6.8, 10.7)	9.6 (8.5, 10.6)	0.04
Blood urea nitrogen (mg/dL)	11 (2, 36)	9 (1, 47)	0.59
Creatinine (mg/dL)	0.7 (0.2, 1.0)	0.6 (0.1, 1.1)	0.58
Total bilirubin (mg/dL)	5.5 (3.9, 10.8)	6.8 (0.7, 17.1)	0.21
Direct bilirubin (mg/dL)	0.4 (0.1, 10.2)	0.4 (0.2, 3.5)	0.37
Creatine phosphokinase (IU/L)	108 (47, 564)	86 (36, 506)	0.25
Albumin (g/dL)	2.6 (1.3, 3.5)	2.7 (2.4, 3.2)	0.42
Hematology			
White blood cell count($x10^9/mm^3$)	12.5 (5.5, 22.7)	13.2 (8.1, 25.0)	0.60
Hematocrit (%)	38 (28, 53)	38 (33, 55)	0.27
Platelet count ($x10^9$ /mm^3)	206 (41, 543)	196 (61, 516)	0.27

Figure 1: Clearance vs. Postmentrual Age



*No relationship between daptomycin CL and postnatal age, gestational age, or postmenstrual age was observed.

Figure 2: Creatinine Phosphokinase Pre and Post Dosing*



*Data represent 2 values (pre/post) from 11 subjects, 1 subject with a pre-dose value, and 1 subject with a post-dose value.

Conclusions

Daptomycin CL in this population of young infants was similar to the CL observed in 2-6 year old children and greater than the CL observed in older children and adults

Young infants may require higher dosing of daptomycin to receive the same drug exposure. The AUC_{24} in adults following a 6 mg/kg dose is 632 µg*h/mL.

There were 24 adverse events reported in 7 (54%) subjects. None were determined to be related to daptomycin. Three were classified as serious adverse events (abnormal abdominal radiograph, pneumatocele, questionable thoracic lesion).

Daptomycin was well tolerated in this small cohort of young infants with no increases in CPK observed after a single dose of the drug.

Additional PK and safety studies are needed to determine the appropriate dosing regimen of daptomycin in this population.

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