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Pharmacokinetics and skin-tissue penetration of daptomycin in rats

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Background: Daptomycin is recommended for complicated skin and skin-structure infections. However, information on the penetration of daptomycin into skin is limited. Therefore, the aim of this in vivo investigation was to determine the pharmacokinetics and skin penetration of daptomycin in rats.

Materials and methods: Concentrations of daptomycin were determined by high-performance liquid chromatography. A noncompartmental pharmacokinetic analysis was conducted to estimate the rate and extent of daptomycin penetration from the systemic circulation into skin tissue. Since protein binding of daptomycin in rat serum was 89.3%, the free maximum concentration (C_{max}) and free area under the curve from time 0 to infinity ($AUC_{0-\infty}$) for plasma were calculated as follows: $fC_{max,\ plasma} = (1 - 0.893) \times C_{max,\ plasma}$, $fAUC_{0-\infty,\ plasma} = (1 - 0.893) \times AUC_{0-\infty,\ plasma}$.

Results: The following values (mean ± standard deviation) were obtained: 0.06±0 L/h/kg for total clearance (CL_{total}), 0.44±0.06 hours for elimination-rate constant, 1.58±0.23 hours for half-life, 0.14±0.02 L/kg for steady-state volume distribution, and 2.28±0.33 hours for mean residence time. Time to C_{max} was 3.0 hours for plasma and skin tissue. C_{max} and $AUC_{0-\infty}$ for plasma were 175.8±5.1 μg/mL and 811.8±31.9 μg × h/mL, respectively. C_{max} and $AUC_{0-\infty}$ for skin tissue were 19.1±1.7 μg/mL and 113.9±21.8 μg × h/mL, respectively. Furthermore, fC_{max} and $fAUC_{0-\infty}$ for plasma were 18.8 μg/mL and 86.9 μg × h/mL, respectively. The degrees of skin-tissue penetration, defined as the $C_{max,\ skin\ tissue}/fC_{max,\ plasma}$ ratio and $AUC_{0-\infty,\ skin\ tissue}/fAUC_{0-\infty,\ plasma}$ ratio, were 1.0 and 1.3, respectively.

Conclusion: Daptomycin exhibited good penetration into skin tissue, supporting its use for the treatment of complicated skin and skin-structure infections. However, further studies are needed in infected patients in order to investigate the relationship between the antimicrobial efficacy of daptomycin and its drug concentrations in skin tissues.

Keywords: daptomycin, pharmacokinetics, rat, skin-tissue penetration

Introduction

Daptomycin is a cyclic lipopeptide antimicrobial agent that exhibits rapid and concentration-dependent bactericidal activity against aerobic and facultative Gram-positive microorganisms.[1] Its spectrum of activity includes susceptible and resistant Gram-positive cocci, including methicillin-resistant *Staphylococcus aureus* and multidrug-resistant *Streptococcus pneumonia*. Arbeit et al reported that daptomycin was effective as a standard therapy for the treatment of complicated skin and skin structure infections caused by Gram-positive pathogens.[2] Daptomycin is recommended for complicated skin and skin-structure infections in clinical practice guidelines by the Infectious Disease Society of America for the treatment of methicillin-resistant *S. aureus* infections.[3] However, information on the penetration of daptomycin into

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skin is limited. The penetration of daptomycin is still a matter of debate, particularly in light of its high plasma protein binding of 92% in humans and its relatively high molecular weight of 1,620 Da.[4] These characteristics limit drug penetration from plasma to tissue. Therefore, the aim of this in vivo investigation was to determine the pharmacokinetics and skin penetration of daptomycin in rats.

Materials and methods

Animal experimentation

This study was reviewed and approved by the Animal Experimentation Committee of Keio University (12056-[0]), and was performed in compliance with its Animal Experimental Guidelines. Ten-week-old male Wistar rats were purchased from Sankyo Labo Service (Tokyo, Japan). Hair from the top of the head was removed using an electric clipper and depilatory cream 4 days prior to the administration of daptomycin. Rats were anesthetized with sevoflurane inhalation. Single-dose plasma pharmacokinetic studies were performed after the subcutaneous administration of 10 mg/mL daptomycin dissolved in saline. Blood samples and skin-tissue samples (10×15 mm), which were removed from the top of the head, were obtained 1, 3, 5, 8, and 12 hours after the subcutaneous administration of daptomycin (50 mg/kg) (three animals per time point). After the skin-tissue sample was weighed, the sample was added to nine times its volume weight of 1% phosphate buffer (pH 6.0).[5] The mixture was homogenized using a Polytron homogenizer to prepare a skin-tissue suspension. The suspension was stored at 4°C for 18 hours to extract daptomycin and then centrifuged (3,000 rpm, 15 minutes).[5] The supernatant was available for measurements of the concentrations of daptomycin.

Measurement of daptomycin concentration

In each sample, 125 µL of plasma and the supernatant obtained from skin tissue was added to 25 µL of mefenamic acid (internal standard) dissolved in methanol and 150 µL of acetonitrile, vortexed for 40 seconds, and centrifuged for 10 minutes at 11,000 rpm.[6] The resulting clear supernatants (20 µL) were injected into high-performance liquid chromatography (HPLC) columns. Total concentrations of daptomycin were determined by the HPLC method of Polillo et al,[6] with minor modifications. The analytical column was a C_8 chromatographic column (BDS Hypersil, 250×4.6 mm, 5 µm; Agilent Technologies, Tokyo, Japan). The ultraviolet wavelength for daptomycin was 214 nm. The mobile phase consisted of 0.1 M phosphate buffer (pH 2.1):acetonitrile:methanol =52:37:11. The lowest concentration of daptomycin was 0.075 µg/mL. The intra- and interday accuracies (as absolute values of the relative errors of the means) and precision (as the coefficient of variation values) were within 10%.

Pharmacokinetic analysis

A noncompartmental pharmacokinetic analysis was conducted to estimate the rate and extent of daptomycin penetration from the systemic circulation into skin tissue. Maximum concentration (C_{max}) was defined as the observed maximum concentration of daptomycin, and T_{max} was the time to C_{max}. The area under the drug concentration–time curve from 0 to infinity ($AUC_{0-\infty}$) and mean residence time (MRT) were calculated based on the trapezoidal rule. Using plasma-concentration data, total clearance (CL_{total}) was estimated as dose (50 mg/kg)/$AUC_{0-\infty}$, and the volume of distribution at a steady state (V_{ss}) was calculated as $CL_{total} \times MRT$. The elimination half-life ($t_{1/2}$) was estimated by

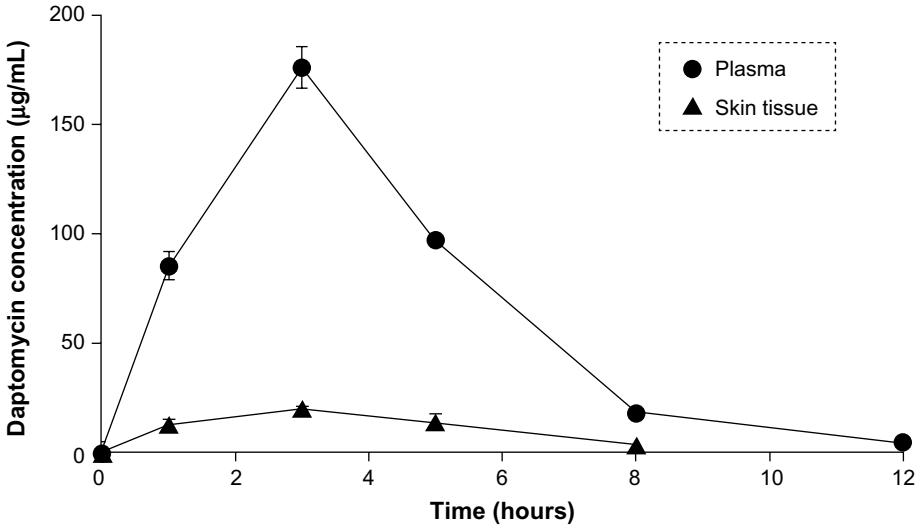

Figure 1 Observed plasma and skin-tissue concentrations of daptomycin in rats after its single subcutaneous administration (50 mg/kg, n=3).

Table 1 Pharmacokinetic parameters of daptomycin in rats after its single subcutaneous administration (50 mg/kg, n=3)

Dose (mg/kg)	CL_{total} (L/h/kg)	K_e ($hours^{-1}$)	$t_{½}$ (hours)	V_{ss} (L/kg)	MRT (hours)	C_{max} (μg/mL)		$AUC_{0-\infty}$ (μg × h/mL)	
						Plasma	Skin tissue	Plasma	Skin tissue
50	0.06±0	0.44±0.06	1.58±0.23	0.14±0.02	2.28±0.33	175.8±6.3	20.1±2.2	811.8±31.9	113.9±21.8

Abbreviations: CL_{total}, total clearance; K_e, elimination-rate constant; $t_{½}$, elimination half-life; V_{ss}, steady-state volume distribution; MRT, mean residence time; C_{max}, maximum concentration; $AUC_{0-\infty}$, area under the plasma concentration–time curve from 0 to infinity.

dividing 0.693 by the elimination-rate constant K_e (CL_{total}/V_{ss}). Since protein binding of daptomycin in rat serum was previously reported to be 89.3%,[7] the free C_{max} and free $AUC_{0-\infty}$ for plasma were calculated as follows: $fC_{max,\ plasma} = (1–0.893) \times C_{max,\ plasma}$, and $fAUC_{0-\infty,\ plasma} = (1–0.893) \times AUC_{0-\infty,\ plasma}$.

Results

The observed concentrations of daptomycin in plasma and skin are shown in Figure 1. Skin-tissue concentrations 12 hours after the administration of daptomycin were not detectable. The following values (mean ± standard deviation) were obtained: 0.06±0 L/h/kg for CL_{total}, 0.44±0.06 $hours^{-1}$ for K_e, 1.58±0.23 hours for $t_{½}$, 0.14±0.02 L/kg for V_{ss}, and 2.28±0.33 hours for MRT (Table 1). T_{max} was 3.0 hours for plasma and skin tissue. C_{max} and $AUC_{0-\infty}$ for plasma were 175.8±6.3 μg/mL and 811.8±31.9 μg × h/mL, respectively (Table 1). C_{max} and $AUC_{0-\infty}$ for skin tissue were 20.1±2.2 μg/mL and 113.9±21.8 μg × h/mL, respectively (Table 1). Furthermore, fC_{max} and $fAUC_{0-\infty}$ for plasma were 18.8 μg/mL and 86.9 μg × h/mL, respectively. The degrees of skin-tissue penetration, defined as the $C_{max,\ skin\ tissue}/fC_{max,\ plasma}$ ratio and $AUC_{0-\infty,skin\ tissue}/fAUC_{0-\infty,\ plasma}$ ratio, were 1.0 and 1.3, respectively.

Discussion

Previous studies on the rat pharmacokinetics of daptomycin in plasma showed that the $AUC_{24\ h}$ of daptomycin was 558 μg × h/mL at an intraperitoneal dose of 30 mg/kg/day,[7] and 605 μg × h/mL at a subcutaneous dose of 40 mg/kg/day, while its $t_{½}$ was 1.6–2.9 hours.[8] As shown in Table 1, our results were consistent with these findings. However, the detailed pharmacokinetic parameters of daptomycin were not shown in previous studies, and its penetration into skin tissue was not evaluated. In the present study, we showed that the $C_{max,\ skin\ tissue}/fC_{max,\ plasma}$ ratio and $AUC_{0-\infty,\ skin\ tissue}/fAUC_{0-\infty,\ plasma}$ ratio were 1.0 and 1.3, respectively (Table 1), and skin-tissue concentrations were equal to free plasma concentrations. Kim et al studied the penetration of daptomycin into soft tissues in healthy subjects with in vivo microdialysis.[9] They showed that the degree of tissue penetration (defined as the $AUC_{tissue}/fAUC_{plasma}$ ratio) was 0.74, and concluded that intravenous daptomycin penetrated well into the tissues, with a tissue concentration of 74% of free plasma concentration. They also mentioned that daptomycin protein binding to serum albumin had been shown to be weak (dissociation constant =90.3 μM) and reversible, which may contribute to the greater penetration estimated from free drug concentrations in plasma. Our results were consistent with these findings, and thus we consider that skin-tissue concentrations are almost equal to free plasma concentrations after daptomycin injection.

In conclusion, daptomycin exhibited good penetration into skin tissue, supporting its use for the treatment of complicated skin and skin-structure infections. However, further studies are needed in infected patients in order to investigate the relationship between the antimicrobial efficacy of daptomycin and its drug concentrations in skin tissues.

Disclosure

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