Effect of Glucose Concentration on the Stability of Daptomycin in Peritoneal Solutions

Daptomycin is a cyclic lipopeptide with rapid concentration-dependent bactericidal activity against almost all gram-positive pathogens (1). Intraperitoneal daptomycin administration in 1.5% and 2.5% glucose solutions has been effective in treating vancomycin-resistant *Staphylococcus* or *Enterococcus* peritonitis in peritoneal dialysis (PD) patients without a relapse or repeated peritonitis subsequently developing (2–7).

Daptomycin has been reported to degrade in 5% glucose solutions at a rate of 15% – 20% per 24 hours at room temperature (8). The saline concentration of PD solution can also have a significant impact on daptomycin stability (8). As previously reported, daptomycin is stable for 4 hours in a solution of 5% glucose in water, but for only 2.5 hours in a solution of 5% glucose in 0.45% saline at room temperature.

Little is known about stability of daptomycin in PD solution. The stability of daptomycin has recently been studied in 3 PD solutions respectively containing 1.36% glucose, icodextrin, and 1.1% amino acids (9), and daptomycin has been found to be stable in 1.36% glucose solution for at least 24 hours and in 1.1% amino-acid solution for more than 168 hours at 25°C. In both cases, the stability of daptomycin declines by more than 10% after 6 hours at 37°C.

The objective of the present work was to study the dependence of daptomycin stability on the glucose concentration in glucose PD solutions held in polyvinylchloride containers at 25°C and 37°C. The chemical stability of daptomycin was also evaluated in icodextrin PD solution.

METHODS

Daptomycin (Cubicin: Novartis, Basel, Switzerland) was obtained as dry powder. The drug was resuspended in 10 mL sterile distilled water and stored at 4°C until use. Three different commercially available solutions for PD were tested: Physioneal 35 (1.36% glucose, 2.0 L bags, 7.5 pH for the mixed solution), Physioneal 35 (2.27% glucose, 2.0 L bags, 7.5 pH for the mixed solution), and Extraneal (2.0 L bags, 5.5 pH) (all solutions: Baxter Healthcare Corporation, Deerfield, IL, USA). One daptomycin concentration was tested in three different bags of each PD solution. After removal of the overwrap from each solution bag, daptomycin was injected through the medication port into the glucose or icodextrin compartment to obtain a final daptomycin concentration of 20 mg/L in each solution bag. The bags were inverted several times to ensure proper mixing and were stored at two temperatures (25°C and 37°C) in a climatic test system (Vötsch Industrietechnik, Balingen, Germany) held at 60% relative humidity. Samples were withdrawn from the stored bags either at 0, 1, 2, 4, and 6 hours after addition of the daptomycin (bags held at 37°C) or at 0, 8, and 24 hours after addition of the daptomycin (bags held at 25°C).

In addition, daptomycin stability was evaluated at ambient temperature and in the same concentration in two other intravenous solutions containing glucose and no other excipients: Glucosada Grifols 5% (Grifols, Barcelona, Spain) and Viaflo Glucosa 10% (Baxter Healthcare Corporation). Samples were withdrawn from these bags at 0, 0.5, 6, and 24 hours after addition of the daptomycin.

Daptomycin concentrations were measured using high-performance liquid chromatography with ultraviolet detection. The chromatographic system consisted of an Agilent 1200 SL pump, an autosampler, and a photodiode array detector. Chromatographic separations were achieved using a Gemini reverse-phase C18 column (150×4.6 mm, 5 μm: Phenomenex, Torrance, CA, USA) and a Gemini C18 guard column with the same package. Reagents for all assays met high-performance liquid chromatography grade. Standard working solutions were prepared from daptomycin stock solutions by serial dilution to yield final concentrations of 1, 2.5, 10, 25, 50, 100, and 500 μg/mL. The (within-day) precision of the method was determined at four concentration levels (1, 3, 60, 300 μg/mL) to represent the low, medium, and high ranges of the calibration curve. Correlation coefficients (r) were better than 0.995 for the calibration curves. The assay was reproducible, with a between-day coefficient of variation of 12.98%.

The average and standard deviation of three bags were calculated at each sample time. For each analysis, the last time point at which drug concentrations exceeded 90% of baseline were used to denote stability.

RESULTS

All solutions were clear in appearance, and no color change or precipitation was observed throughout the

study. For each combination tested, no changes in the physical parameters of solutions (pH, particulate matter, or visual appearance) were observed (data not shown).

Table 1 reports the mean daptomycin concentration measured for each PD solution. In Physioneal, for the two glucose concentrations tested, more than 90% of the initial dose of daptomycin remained available for up to 24 hours at 25°C and within 6 hours at 37°C. The percentage daptomycin dose remaining was similar in Physioneal 1.36% (up to 96%) and Physioneal 2.27% (up to 92%). No effect of temperature on daptomycin stability was observed.

To demonstrate the dependency on glucose concentration of daptomycin recovery for the lowest concentration, samples with increasing glucose concentration values (5% and 10%) were prepared. Daptomycin recovery correlated with decreasing glucose concentration—an effect that became more apparent during storage (Table 1).

In Extraneal, we observed high variability between the three measurements, with the concentrations being under the limit of quantitation in some cases. For that reason, we decided to exclude Extraneal solution from the study.

TABLE 1
Daptomycin Concentrations Over Time in Selected Peritoneal Dialysates Held in Polyvinylchloride Containers at Various Temperatures

Solution	Temperature	Holding time (h)	Daptomycin Concentration (µg/mL)	Percentage of initial concentration remaining
Physioneal 1.36%[a]				
	25°C	0	22.468	—
		8	20.819	92.66
		24	20.724	92.24
	37°C	0	23.309	—
		1	23.168	99.39
		2	22.706	97.41
		4	21.951	94.17
		6	21.646	92.86
Physioneal 2.27%[a]				
	25°C	0	23.046	—
		8	22.628	98.19
		24	22.590	98.02
	37°C	0	22.706	—
		1	22.989	101.25
		2	22.847	100.62
		4	21.802	96.02
		6	22.217	97.85
Grifols 5% glucose[b]				
	25°C	0	20.647	—
		0.5	17.644	85.46
		6	15.253	73.88
		24	12.384	59.98
Viaflo 10% glucose[a]				
	25°C	0	14.948	—
		0.5	13.302	88.99
		6	11.359	75.99
		24	8.946	59.85

[a] Baxter Healthcare Corporation, Deerfield, IL, USA.
[b] Grifols International, Barcelona, Spain.

DISCUSSION

The stability of a chemical must be tested in each solution into which it will be mixed, in the type of container in which it will be held, and at room temperature (storage conditions) and body temperature (10–12).

Peyro Saint Paul *et al.* evaluated the stability of daptomycin in some PD solutions containing 1.36% glucose (9). After 24 hours at 25°C, 96.0% of the initial concentration remained, and 102% remained after 6 hours at 37°C. Our results were in agreement, with our samples being stable after 24 hours at room temperature and 6 hours at 37°C.

Over 24 hours, daptomycin concentrations declined similarly in Physioneal 2.27% glucose solution held at 25°C (92%) and 37°C (98%); in Glucosada Grifols 5% and Viaflo Glucosa 10% solutions, they declined (60%) below the level chosen to denote stability. The observed difference in daptomycin recovery can be explained only by the different glucose concentrations of the evaluated solutions. The excipients present in PD solutions have no effect on daptomycin recovery, as can be seen from the results obtained with PD solutions having the same quantitative and qualitative composition (Physioneal 1.36% and 2.27%).

Evaluation of the compatibility of daptomycin in Extraneal has not been determined. The high molecular weight of the icodextrin in Extraneal and the low pH of the solution might explain the large differences observed in daptomycin concentrations measured in samples from identical bags (13). As previously reported (9), the reliability of high-performance liquid chromatography measurements of daptomycin mixed into icodextrin solutions was unacceptable.

CONCLUSIONS

Our results clearly show that daptomycin compatibility is preserved at glucose concentrations of 2.27% or lower, as demonstrated in the case of Physioneal PD solution.

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DISCLOSURES

The authors have no financial conflicts of interest to declare.

Maria Asunción Parra[1]*
Miguel Angel Campanero[1]
Belen Sádaba[1]
Angel Irigoyen[2]
Laura García–López[3]
Maria Jose Fernandez–Reyes[4]
Jose Ramon Azanza[1]

Clinical Pharmacology Service[1]
University Hospital
Department of Organic and Pharmaceutical Chemistry[2]
School of Pharmacy, CIFA
University of Navarre
Pamplona, Spain
Department of Pharmacy[3]
Department of Nephrology[4]
General Hospital of Segovia
Segovia, Spain

*email: mparravi@unav.es

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