2010). This indicates that high serum levels can be reached after intraperitoneal administration.

5. PHARMACOKINETICS AND PHARMACODYNAMICS

Data on pharmacokinetics in various patients are presented in Table 45.4.

5a. Bioavailability

Daptomycin is available for i.v. use only. Daptomycin is highly but reversibly bound to plasma proteins (90–93%), primarily to albumin, as measured by ultracentifugation (Woodworth *et al.*, 1992). The binding is concentration independent, based on determination by equilibrium dialysis (Dvorchik *et al.*, 2003).

The possible effects of this high protein binding are discussed later in section 5c, Clinically important pharmacokinetic and pharmacodynamic features. A two-compartment model with first-order elimination provides the best fit for recording data on daptomycin concentrations in plasma over time (Table 45.5).

5b. Drug distribution

Daptomycin has a relatively small volume of distribution, which is compatible with its characteristics of not crossing cell membranes (no penetration in erythrocytes) (Woodworth *et al.*, 1992) and remaining within plasma and extracellular fluid.

Daptomycin has a relatively long half-life of 8–9 hours. At a dose of 8 mg/kg per 24 hours, the accumulation factor is 1.2. The estimated accumulation factor for a dosage of 8 mg/kg every 12 hours is 1.7, which has been correlated with an increased occurrence of adverse muscle effects associated with twice-daily dosing (Dvorchik *et al.*, 2003).

A single-dose (Woodworth *et al.*, 1992) and two multiple-dose (Benvenuto *et al.*, 2006; Dvorchik *et al.*, 2003) phase I studies were conducted in young healthy adults. Daptomycin pharmacokinetics was generally linear and time independent at doses of 4–12 mg/kg/day. In the first study, 24 healthy subjects received daptomycin (4, 6, and 8 mg/kg of body weight) every 24 hours for 7–14 days. The pharmacokinetic parameters measured on the median day of the study period (day 7) for a dose of 4 mg/kg are shown in Table 45.6.

In subsequent studies, 6 and 8 mg/kg dosing regimens were repeated, and 10 and 12 mg/kg/day regimens were explored for up to 14 days (Benvenuto *et al.*, 2006). The data at steady state in the two studies for the regimens (6 and 8 mg/kg on days 7 and 4, respectively) are combined in Table 45.6. The data for 10 and 12 mg/kg/day are from the second study. For approved doses of 4–6 mg/kg, the half-life was 7.9–8.9 hours, the volume of distribution approximately 0.1 l/kg, and the plasma clearance approximately 8.1–9.1 ml/h/kg. Steady-state trough concentrations (C_{min}) were reached by the third daily dose. The mean (± standard deviation) steady-state trough concentrations attained after administration of 4, 6, 8, 10, and 12 mg/kg once daily were 5.9 (1.6), 6.7 (1.6), 10.3 (5.5), 12.9 (2.9), and 13.7 (5.2) mg/l, respectively (Package Insert, 2007).

Although daptomycin does penetrate into the lung, it is known to interact *in vitro* with pulmonary surfactant, resulting in inhibition of antibacterial activity. This effect was specific to daptomycin and is consistent with its known mechanism of action. This represents the first example of

Table 45.5. Summary of pharmacokinetic parameters (median values) sorted by estimated creatinine clearance (CL_{CR}) and obtained by Bayesian estimation from the final calculated model.

CL_{CR}	$AUC_{0-\infty}$ [a] (µg/h/ml)	Clearance (l/h)	V_{SS} (l)	Half-life (h)
> 80 ml/min (*n* = 165)	400.77	0.86	9.73	8.28
< 80 to > 40 ml/min (*n* = 80)	436.54	0.64	8.75	9.07
≤ 40 ml/min (*n* =16)	716.24	0.37	10.36	18.96
On dialysis (*n* = 21)	1205.60	0.24	10.44	29.32

[a]Calculated for a single 4 mg/kg dose.

Abbreviations: AUC: area-under-the-concentration-time curve; V_{ss}: volume of distribution at steady state.

Adapted from Dvorchik *et al.* (2004).

Table 45.6. Pharmacokinetic parameters of daptomycin in healthy volunteers at steady state after administration of multiple intravenous doses.

Dose (mg/kg)	C_{max} (mg/l)	AUC_{0-24} (µg/h/ml)	CL_{tot} (ml/h/kg)	V_{SS} (l/kg)	Half-life (h)
4 (*n* = 6)	57.8 (3.0)	494 (75)	8.3 (1.3)	0.096 (0.009)	8.1 (1.0)
6 (*n* = 6)	93.9 (6.0)	632 (78)	9.1 (1.5)	0.101 (0.007)	7.9 (1.0)
8 (*n* = 6)	123.3 (16.0)	858 (213)	9.0 (3.0)	0.101 (0.013)	8.3 (2.2)
10 (*n* = 9)	141.1 (24.0)	1039 (178)	8.8 (2.2)	0.098 (0.017)	7.9 (0.6)
12 (*n* = 9)	183.7 (25.0)	1277 (253)	9.0 (2.8)	0.097 (0.018)	7.7 (1.1)

Abbreviations: C_{max}: peak serum concentration; AUC: area-under-the-concentration-time curve; CL_{tot}: total clearance; V_{SS}: mean volume of distribution at steady state.

Adapted from Package Insert (2007) based on data from Dvorchik *et al.* (2003) and Benvenuto *et al.* (2006).