Some *in vitro* studies on these combinations are discussed in more detail in the specific paragraphs regarding clinical uses.

5d. Excretion

Renal clearance is the most important route of elimination. In a population pharmacokinetic analysis, data from subjects in nine phase I (n = 153) and six phase II/III (n = 129) clinical trials were combined to identify factors contributing to interindividual variability in daptomycin pharmacokinetics. Over 30 covariates were considered. A two-compartment model with first-order elimination provided the best fit for data on daptomycin concentrations in plasma over time. In the final population pharmacokinetic model, renal function contributed most significantly to interindividual variability. CL varied linearly with the estimated creatinine clearance (Table 45.5).

Clearance among dialysis subjects is approximately one third that of healthy subjects (0.27 vs. 0.81 l/h). The relationship between body weight and the rate and extent of extravascular distribution supports the dosing of daptomycin on a milligram per kilogram of body weight basis. Renal clearance should determine the dosage interval (Dvorchik *et al.*, 2004).

The limited systemic clearance is consistent with high protein binding. After administration of 1 mg/kg of carbon-14–labeled daptomycin, recovery of carbon-14 in urine and feces accounted for 83% of the administered dose, with the greatest fraction (78%) appearing in the urine. Specific analysis for daptomycin in both urine and plasma indicated that metabolic products were present in urine, but total carbon-14 in plasma consisted of daptomycin only (Woodworth *et al.*, 1992). Mean urinary recovery of unchanged daptomycin was 47–60% of the dose at 24 hours after administration of 4 or 6 mg/kg in healthy young adults (Dvorchik *et al.*, 2003).

In a study by Woodworth *et al.* (1992), a small proportion of daptomycin (5.0%) was recovered from feces (collected for up to 6 days) based on total radioactivity.

No metabolites were detected in the plasma on day 1 after administration of daptomycin (6 mg/kg) to subjects. The site of metabolism of the inactive metabolites detected in urine has not been identified (Package Insert, 2007).

Clearance appears to be more rapid in children. The pharmacokinetics of a single 4 mg/kg i.v. dose of daptomycin over 24 hours was studied in 25 children (12–17 years, n = 8; 7–11 years, n = 8; 2–6 years, n = 9) with suspected or proven Gram-positive infections receiving standard therapy in a multicenter open-label study. Daptomycin systemic exposure decreased with decreasing age, reflecting more rapid rates of clearance in younger children. Total body exposure estimates in adolescents were approximately 1.7 times those observed in children < 6 years of age (374.4 vs. 215.3 mgh/l) and were similar to those observed in adult historic controls. Estimates of apparent elimination half-life averaged 6.7 hours in adolescents, 5.6 hours in children 7–11 years of age, and 5.3 hours in children < 6 years of age (Abdel-Rahman *et al.*, 2008). The lower exposure as compared with adults is also described for children aged 3–24 months (Bradley *et al.*, 2014). In children 2–6 years of age receiving doses of 8 and 10 mg/kg, the exposures were 429 and 549 mgh/l, respectively. These exposures are still lower compared with the exposure in 12 healthy volunteers after a 6 mg/kg dose (690 mgh/l) (Chakraborty *et al.*, 2009) but are comparable to the exposure in 13 healthy Taiwanese volunteers (470 mgh/l) (Liang *et al.*, 2009).

5e. Drug interactions

In vitro experiments using human hepatocytes demonstrated that daptomycin has no effects on hepatic cytochrome 450–mediated drug metabolism and therefore suggest that daptomycin is unlikely to show potential for pharmacokinetic interactions with concomitantly administered drugs that are metabolized by cytochrome P450 isoforms (Oleson *et al.*, 2004). Drug interaction single- and multiple-dose studies were performed in healthy subjects. No clinically relevant interactions were found when daptomycin, 2–6 mg/kg, was administered with aztreonam, tobramycin, warfarin, simvastatin, and probenecid (Package Insert, 2007).

Although no specific drug interactions have been detected when daptomycin is co-administered with hydroxymethylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors (e.g. simvastatin), both daptomycin and statins may increase creatine phosphokinase (CPK) levels. Therefore, it is suggested by the manufacturer to withhold statin therapy during therapy with daptomycin. Fowler *et al.* (2006) reported a number of patients who developed CPK increases in a study of daptomycin efficacy in *S. aureus* bacteremia/endocarditis and were receiving concomitant HMG-CoA reductase inhibitors. Parra-Ruiz *et al.* (2012b) concluded based on 36 patients receiving both drugs and 68 patients receiving only daptomycin (mean dose 7.8 mg/kg/day for mean duration of 17 days) that concomitant administration of daptomycin and statins is safe and is not associated with an increased risk of rhabdomyolysis. Berg *et al.* (2014) performed a retrospective cohort study of patients ≥ 18 years of age who received daptomycin for ≥ 72 hours and had ≥ 1 followup CPK level tested during a 5-year period. The study included 498 patients; 384 received daptomycin alone with no previous or concurrent exposure to statins, 63 received daptomycin concurrent with statin, and 51 had statin held during daptomycin therapy. Cumulative incidence of CPK elevation was 5.1% and 12% at 7 and 14 days, respectively. Those on daptomycin and statin concurrent therapy demonstrated an approximately twofold risk of CPK elevation compared with those having their statin therapy held, but the overall group effect was not statistically significant (p = 0.17). Although none of these studies showed an increase in CPK in patients treated with both statins and daptomycin, all the authors recommend monitoring these patient closely for increase in CPK.

DRUG–LABORATORY TEST INTERACTIONS

A cluster of patients experiencing elevations of international normalized ratio without clinical bleeding in temporal