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Nicolas Gregoire[1,2], Alexia Chauzy[1], Julien Buyck[1], Blandine Rammaert[1,3], William Couet[1,2*] Sandrine Marchand[1,2].

[1] INSERM, U1070, UFR de Médecine Pharmacie, Université de Poitiers, 1 rue Georges Bonnet, TSA 51106, 86073 Poitiers Cedex 9, France

[2] Laboratoire de Toxicologie-Pharmacocinétique, CHU of Poitiers, 2 rue de la Miletrie, 86000 Poitiers, France

[3] Service de maladies infectieuses et tropicales, CHU of Poitiers, 2 rue de la Miletrie, 86000 Poitiers, France

* Corresponding author. william.couet@univ-poitiers.fr, tel: (33) 5 49 45 43 79

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Abstract

Due to the low level of resistance observed with daptomycin, this antibiotic has an important place in the treatment of severe Gram-positive infections. It is the first in class of the group of calcium-dependent, membrane binding lipopeptide. It is a cyclic peptide constituted of 13 amino acids and a n-decanoyl fatty acid chain. The antibacterial action of daptomycin requires its complexation with calcium.

Daptomycin is not absorbed from the gastrointestinal tract and needs to be administered parenterally. The distribution of daptomycin is limited (volume of distribution of 0.1 L/kg in healthy volunteers) due to its negative charge at physiological pH and its high binding to plasma proteins (about 90%). Its elimination is mainly renal, with about 50% of the dose excreted unchanged in the urine, justifying dosage adjustment for patients with renal insufficiency. Pharmacokinetics of daptomycin is altered under certain pathophysiological conditions, resulting in high inter-individual variability. As a result, therapeutic drug monitoring (TDM) of daptomycin may be of interest for certain patients such as intensive care unit (ICU) patients, patients with renal or hepatic insufficiency, dialysis patients, obese patients or children. A target for the ratio of the area under the curve to the minimum inhibitory concentration (AUC/MIC) greater than 666 is usually recommended for clinical efficacy, whereas in order to limit the risk of undesirable muscular effects the residual concentration (Cmin) should not exceed 24.3 mg/L.

Key points:

Daptomycin is highly bound to plasma proteins (90%) and it’s unbound fraction may vary considerably between patients with strong impact on its pharmacokinetics.

This protein binding of daptomycin should be considered for patients with renal failure, including dialysis patients, as well as children.

1 Introduction

Daptomycin is the first calcium-dependent membrane binding lipopeptide. It was isolated in the 1980s, and found to have impressive activity against Gram-positive, but not Gram-negative bacteria. [1] However, Eli Lilly and Company (Lilly) suspended clinical investigation of daptomycin in 1991 because of skeletal muscle toxicity observed at high doses (4 mg/kg every 12h). [2] In 1997, Cubist Pharmaceuticals, Inc. (Cubist) licensed worldwide rights for daptomycin from Lilly. Yet due to the emergence of multidrug resistant bacteria, daptomycin was revisited. Its side effects were minimized by changing its dosing regimen and it received approval from the U.S. food and drug administration (FDA) in 2003. Initial FDA authorization was for complicated skin and skin structure infections (cSSSI) in adult and paediatric patients > 1 year old, and *Staphylococcus aureus* bloodstream infections, including those with right-sided infective endocarditis in adults. Due to low resistance rate, low frequency of side effects and convenient once-a-day administration, daptomycin is currently widely used for *Staphylococcus* spp. and *Enterococcus* spp. infections. [3]

2 Chemistry

Daptomycin is produced as a minor component of a complex lipopeptide mixture by the soil actinomycete *Streptomyces roseosporus*.[4] It is a cyclic peptide constituted of 13 amino acids and a n-decanoyl fatty acid chain at the N-terminus with a 1620.7 g/mol molecular weight (Figure 1). It has 4 acids residues (pK_a of 1.3, 3.8, 4.1 and 4.4) and 2 basic residue (pK_a of 1.3 and 10.7), resulting in a total molecular charge of -3 at neutral pH (the basic residue with pKa of 1.3 is unionized at neutral pH). [5, 6]. The negative charge at neutral pH contributes to its high solubility in water (17.3 mg/L, logP = -5).[7, 8] and its lipophilic tail contributes to its amphiphilic character. As a result of its negative charge, daptomycin aggregates into

oligomeric structures with calcium, which enables the interaction of the lipophilic tail of daptomycin with the bacterial cell membrane, a prerequisite of its antimicrobial activity [5].

3 Mechanism of action

Daptomycin is a membrane-active peptide active against Gram-positive bacteria.[9] The presence of calcium ions at physiological concentrations (1.25 mM) is a prerequisite for the antibacterial activity of daptomycin, by masking the overall negative charge and stimulating oligomerization of daptomycin.[1, 10] The Ca^{2+}-daptomycin complex has an increased affinity for negatively charged phospholids of cellular membranes, including phosphatidylglycerol. Yet the exact mechanism of action of daptomycin is still debated, it is admitted that it displays a rapid bactericidal activity by interacting with the cytoplasmic membrane of the bacteria, leading to an efflux of potassium, which in turn should lead to bacterial death.[11] However, the simple pore formation may not be the primary antibacterial mechanism of daptomycin, and insertion into fluid membrane microdomains, so-called RIFs (regions of increased fluidity), and subsequent rigidification of those regions seems to play a central role. [9].

Furthermore, lipopeptides are known as immunomodulators that interact with pattern recognition receptors such as Toll-like receptors in antigen presenting cells. Daptomycin can also insert into membrane vesicles of immune cells, but further studies are needed to elucidate this possible interaction based on the known immunomodulatory activity of other lipopeptides. [12]

4 Spectrum of activity.

Daptomycin presents a rapid *in vitro* bactericidal effect against a wide spectrum of Gram-positive bacteria including *Staphylococcus aureus* (SA, of which methicillin resistant

Staphylococcus aureus, MRSA), coagulase-negative staphylococci, streptococci (of which penicillin-resistant streptococci), enterococci (of which vancomycin resistant enterococci, VRE), *Peptostreptococcus*, *Clostridium perfringens* and corynebacterium sp. [13]

5 Mechanisms of resistance

The prevalence of *de novo* resistance to daptomycin without prior exposure has been reported to be extremely rare (0.04% in *S. aureus*). [14, 15] However, even if daptomycin is still quite active, resistance to daptomycin has been widely reported over the past years in Staphylococci and Enterococci. Mutations of various genes are involved in these mechanisms of resistance, *e.g*. increase of bacterial membrane positive surface charge, alteration in the bacterial membrane fluidity, increased carotenoid pigment content, and increased teicoic acid synthesis in the cell wall have been described [16] For more details, a review has described previously the mechanisms and genes involved in resistance to daptomycin. [17]

Depending on the bacteria, two main mechanisms of resistance are used to develop resistance to daptomycin. With *Enterococcus faecalis* the mechanism corresponds to diversion of the antibiotic from the preferential binding site of daptomycin at the septum of the bacteria, resulting in ineffective binding of daptomycin. With *Staphylococcus aureus* and *Enterococcus faecium*, the mechanism is a modification of charge of the cell membrane leading to electrostatic repulsion of the positively charged complex daptomycin-Ca^{2+}. Noticeably with Staphylococci, daptomycin resistance is generally observed in high-inoculum infections like endocarditis and abscesses when insufficiently high low doses are used.[18-20] Furthermore, the vancomycin-intermediate *S. aureus* (VISA) phenotype is also linked to increased resistance to daptomycin during therapy. [21] This cross-resistance is likely induced by modifications in the same molecular pathways. [17]

6 Indications approved in the marketing authorization

Daptomycin is used to treat skin infections, bloodstream infections, right-sided endocarditis, sepsis and urinary tract infections caused by Gram-positive bacteria, such as *S. aureus*, both methicillin-susceptible and -resistant (MSSA and MRSA), as well as several *Streptococcus* and *Enterococcus* species. [22]

7 Pharmacokinetic/Pharmacodynamic indices and breakpoints

It was shown that area under the curve/MIC (AUC/MIC) ratio is the pharmacokinetic/pharmacodynamic (PK/PD) index that best correlates with daptomycin activity.[23] According to target values used by the EUCAST to determine breakpoints, AUC/MIC ratios needed for bacteriostatic or bactericidal effects are >438 or >1061. [24-26] Although antimicrobial activity depends on unbound antibiotic concentrations, these targets were estimated in mice with thigh infection and rely on total concentrations. Yet since the average unbound fraction (fu) in mice and human are comparable (about 10%), these targets can be used in human. However because it is extensive, even a minor modification of daptomycin protein binding may have a major effect on fu, which may therefore vary widely between subjects or/and due to concentration dependent or disease related effect. [23, 27] This protein binding issue could therefore possibly explain that in some cases no link was established between PK/PD indices and clinical efficacy [28] while in other cases the link was U-shaped [29]. Yet, in a clinical study with 35 patients, the ratio AUC/MIC>666 was associated with statistically reduced mortality[30] and in another study, a residual total concentration (Cmin) of less than 3.2 mg/L was associated with reduced efficacy. [31]. At that point the clinical relevance of these target values based on total concentrations is not guarantee.

Clinical breakpoints have been fixed by EUCAST at 1 mg/L for *Staphylococcus* spp. and *Streptococcus* spp. (except *S. pneumonia* for which the use of daptomycin is not recommended). [32] The EUCAST did not determined clinical breakpoint for *Enterococcus spp.* but determined epidemiological cut-off values of 4 mg/L for *E. faecalis* and 8 mg/L for *E. faecium*, whereas the Clinical and Laboratory Standards Institute (CLSI) determined a susceptible breakpoint of <2 mg/L for *E. faecalis* and a separate susceptible dose-dependent breakpoint of <4 mg/L for *E. faecium*.[33]

Regarding toxicity, a total trough concentration (Cmin) of daptomycin >24.3mg/L was shown to be associated with an increased probability of creatine phosphokinase (CPK) elevation. [2, 3, 34, 35] However, for some authors this threshold could be exceeded without increasing the risk of toxicity.[36]

8 Bioanalysis

Chromatographic Methods. Chromatographic methods for the determination of daptomycin in plasma [27, 30, 37-41], dry plasma spots [40], serum [42], whole blood [43], urine [27, 37, 38], plasma ultrafiltrate [27], and peritoneal fluid [37] can be found in the literature.

Methods using UV detection have quantitation limits ranging from 2 to 5 mg/L [30, 38, 41, 42], higher than those using mass detection with positive electrospray ionization, with quantitation limits ranging from 1 to 2 mg/L in plasma and of 0.05 mg/L in plasma ultrafiltrate. [27, 37, 39, 43, 44] Another characteristic of LC-MS/MS methods is that they allow the use of small test samples (50µL), which can be an advantage for concentrations determinations in paediatrics.[44]

Stability. Because of temperature dependent proteases activity, daptomycin is unstable in serum at body temperature and decreases by more than 50% after only 24h. [45] However, daptomycin is stable at room temperature in whole blood and in plasma for at least 2 h and 6 h

respectively. [44] Concentration loss in serum at room temperature is approximately 5% after 12h and more than 10% after 24 h. [45] Concentrations in serum samples stored at 4°C decrease by 10% after 7 days. [45] Daptomycin is stable in stock solution and in plasma for at least one year at -20°C, it is also stable after 3 freeze/thaw cycles.[39, 42, 44] After extraction, daptomycin is stable in auto-sampler at room temperature for at least 6 h. [39, 44]

Protein binding estimation. Protein binding of daptomycin can be determined by ultracentrifugation. [46], ultrafiltration [27], or microdialysis [47]. As daptomycin adheres to ultrafiltration membranes, non-specific binding should be assessed. Furthermore non-specific binding reported in the literature increases as concentrations decrease, ranging from 5% for concentrations of 70 mg/L to 75% for concentrations of 1 mg/L. This relationship between the concentration of daptomycin and non-specific binding must be taken into account when correcting the concentrations measured in the ultra-filtrates. [27, 47]

9 Clinical pharmacokinetics

9.1 Dosage regimens approved in the marketing authorization

It is indicated that daptomycin should be administered once daily as a 30-min infusion at a dose of 4 mg/kg/day (complicated skin and soft tissue infections) or 6 mg/kg/day (other indications). In case of renal insufficiency (creatinine clearance<30 mL/min), the interval of dose should be extended to 48h. At initiation of treatment, and then at least once weekly, CPK levels should be measured in order to monitor the occurrence of muscular adverse events. [48]

EMA and FDA approved the use of daptomycin for treatment of paediatric patients with complicated skin and soft tissue infections (cSSTI) at dosages of 5, 7, 9, and 10 mg/kg every 24 h for patients aged 12-17, 7-11, 2-6, and 1-2 years old, respectively [48, 49] and at dosages of 7, 9, and 12 mg/kg every 24 h for patients aged 12-17, 7-11, and 1-6 years old, respectively for treatment of *S. aureus* bacteraemia [48, 50]. Due to peak concentration toxicity observed

in preclinical studies, it is recommended to extend the infusion time from 30 min to 1 hour for children under 11 years of age.[48-50]

9.2 Absorption

Due to its very low lipophilicity (logP=-5), daptomycin is poorly absorbed orally with >90% excreted in the faeces in animal models.[13] There is no clinical information about subcutaneous administration but in animals a relatively high bioavailability was observed using this route of administration. [13] Peritoneal, intrathecal or intraventricular administration of daptomycin were also used. [51, 52]

9.3 Distribution

The extravascular distribution of daptomycin is limited due to its negative charge at physiological pH, its low lipophilicity and its high binding to plasma proteins. The volume of distribution of total daptomycin is around 0.1 L/kg for healthy volunteers.[53, 54].

Daptomycin is substrate of the efflux transporter p-glycoprotein (P-gp). [55] In patients (n=81) with bone and joint infection, the volume of distribution of daptomycin was reported to be 25% lower in individuals having the CGC/CGC haplotype for *pgp* compared with any other haplotype, which, according to the authors, could be due to a greater efflux of certain tissues.[56] However, in another study conducted on 12 healthy volunteers, neither rifampicin administration nor *pgp* single nucleotide polymorphism were associated with significant differences in daptomycin disposition.[57]

Distribution within cells. *In vitro,* it has been shown that daptomycin can penetrate within cells, with a 60% ratio between intracellular and extracellular concentration in neutrophils. [55, 58] However, it was shown in mice that achievable plasma levels were insufficient to eliminate an intracellular strain of MRSA. [59]

Distribution into soft tissue interstitial fluid. After administration of daptomycin at 4 mg/kg it has been shown in healthy volunteers and diabetic patients that daptomycin diffuses into the soft tissue interstitial fluid, with concentrations in the range of 70 to 90% of free plasma concentrations. [47]

Distribution within lung. While daptomycin is effective against *S. pneumoniae in vitro*, this does not translate *in vivo* into sufficient therapeutic activity for treatment of lung infections. This may be due to a weak distribution of daptomycin in the lungs, but also to its sequestration by lung surfactant, which contains phosphatidylglycerol..[60] For now, information regarding lung distribution is missing.

Distribution within central nervous system. After IV infusion of daptomycin 10 mg/kg to patients with meningitis, daptomycin has a minimal penetration into central nervous system (<1% which was corrected to 11.5% after accounting for protein binding). [52, 61] By contrast, daptomycin can be an effective treatment option via intrathecal or intraventricular administration when neurosurgical access is available. [52]

Distribution into peritoneal fluid. After IV administration, Gika et al. reported good daptomycin distribution within peritoneal fluid, although the ratio between area under the curve (AUC) was not indicated.[37] Intraperitoneal administration of daptomycin has been reported for peritoneal dialysis patients with peritonitis. [51, 62, 63] A 300 mg dose allowed to reach effective concentrations in dialysate, and the systemic bioavailability was high (70%). However, this should be considered with caution since peritonitis may have increase peritoneal permeability and thus increase the bioavailability. [51]

Distribution into bone and synovial fluid. The penetration of daptomycin into bone is good, with a ratio of unbound AUC of daptomycin in bone and plasma of about 1. [64] This makes daptomycin an attractive antibiotic for treatment of staphylococcal prosthetic joint infection.

[65] Similarly, bone penetration has been shown to be sufficient for the treatment of the diabetic foot infections. [66, 67]

Cardiac distribution. Daptomycin is used for the treatment of infectious endocarditis due to its good diffusion within the vegetations [68] as well as at the level of the cardiac valves [69].

9.4 Elimination

Daptomycin is primarily eliminated by the kidney. In a radiolabelled study in healthy volunteers, 78 % of the dose was recovered in urine, of which 52% were biologically active; the rest was proposed to be peptide fragments produced during renal excretion or within urinary bladder. [13, 46] Indeed, the kidney is known to be an active site of peptide degradation due to the presence of peptidases, and it can be noted that in rats, high concentrations of daptomycin have been found in the kidneys where it can be degraded. [70, 71] Based on PK results in healthy volunteers, unbound renal clearance of daptomycin can be estimated to vary between 60 and 80 mL/min, which is less than the glomerular filtration rate and therefore suggests tubular reabsorption.[54] It is of note that probenecid had no effect on the PK of daptomycin, suggesting that organic anion transporters (OAT) are not involved in renal elimination of daptomycin. [13]

Non-renal elimination of daptomycin does not involve cytochrome P450 enzymes, and preclinical PK studies indicated that daptomycin does not appear to inhibit or induce any of the key cytochrome P450 isoenzymes. [13] In healthy volunteers, after IV administration of radiolabelled daptomycin (^{14}C-daptomycin), 5% of the ^{14}C dose was recovered in faeces.[46] It has been shown in a clinical case that after administration of daptomycin at 8 mg/kg/day the concentrations of daptomycin in bile were comparable to those in plasma.[72]

9.5 Drug-drug interactions

Since daptomycin has little or no metabolism by cytochrome P450, metabolic drug-drug interactions are unlikely. On the other hand, its renal elimination poses a possible risk of decreased clearance when given concomitantly with drugs that reduce glomerular filtration rate, such as non-steroidal anti-inflammatory drugs.[13]

So far, no interactions requiring precautionary measures have been reported due to its high protein binding.

9.6 Protein binding.

In plasma, daptomycin binds reversibly and primarily to albumin with an averaged bound fraction of about 90-95% in healthy volunteers. [46, 73] This high protein binding would justify to measure unbound concentrations, which can be done by different methods but which is complicated by the fact that daptomycin binds to the separation membranes (see bioanalysis section). If measurement of free concentrations is not possible, at least the factors that may alter protein binding should be considered. In that respect, it was shown that the fraction of daptomycin bound to proteins in plasma depends little on the level of daptomycin concentrations but increases with albuminemia. [27] A change in protein binding has theoretically no effect on average free drug concentration at steady-state, but it does affect average total concentration at steady-state. [74-76] Thus, while the total concentration at steady-state (Css) depends on the free fraction (f_u) and on the clearance of unbound concentration (CL_u) (Eq.1), the unbound concentration at steady-state (Css_u) is independent of fu (Eq.2):

$$Css = \frac{\text{Daily dose}}{CL} = \frac{\text{Daily dose}}{f_u \times CL_u} \quad \text{(Eq.1)}$$

$$Css_u = f_u \times Css = \frac{\text{Daily dose}}{CL_u} \quad \text{(Eq.2)}$$

Thus, the area under the curve of free concentrations (AUC_u), which is the parameter related to the efficacy of daptomycin, is also independent of f_u (Eq.3).

$$AUC_u = Css_u \times \text{Dosing Interval} = \frac{\text{Daily dose} \times \text{Dosing Interval}}{CL_u} \quad \text{(Eq.3)}$$

Since daptomycin is strongly bound a relatively small change in protein binding (eg: from 90% to 95%) will have a much higher effect on fu (in that case from 10% to 5%). As an illustration, in a study in intensive care unit (ICU) patients with variable renal function, the f_u varied by 8 fold between patients (from 4% to 33%). Therefore, different values of total concentrations may correspond to the same free concentration (Eq.2). For example, in case of low albuminemia (and high f_u), a low total concentration of daptomycin could lead to the erroneous belief that a patient is underdosed. [27] *In vitro*, the presence of calcium at physiological concentrations increases the binding of daptomycin to serum albumin from 85% to 96%. [73] It is therefore important to control calcium concentration when performing protein binding experiments with daptomycin. The clinical impact of this observation has not been evaluated. Finally, it should be noted that *in vitro,* the effective concentration could differ from the free concentration.[77] Whether this is confirmed *in vivo* remains to be established.

9.7 PK in healthy volunteers

In healthy volunteers, when considering total concentrations, daptomycin has a volume of distribution of ~0.1 L/kg (7 L), a systemic clearance of ~8-10 mL/h/kg (0.56-0.70 L/h=9.3-11.7 mL/min), a fraction of dose excreted unchanged in urine of ~54%, a protein binding of ~92%, a half-life ($t_{1/2}$) of ~8-9 h. [53, 54] Daptomycin PK is almost linear in the 4 to 12 mg/kg dose range, regarding AUC, peak concentration (Cmax) and Cmin levels. [53, 54, 78] After daptomycin administration as a bolus (10 s or 2 min), the AUC and the Cmin were

equivalent to those obtained after administration as a 30 min infusion. [78, 79] However, after the bolus, the Cmax was higher than after the 30-minute infusion

9.8 PK in special populations

It should be noted that, due to the difficulty of measuring free concentrations, most studies in special populations have been conducted using total concentrations, making interpretation more difficult.

Renal impairment. Clearance and therefore AUC decrease while and $t_{1/2}$ increases with decreasing renal function. [27, 80-82] Compared with critically ill patients with normal renal function (creatinine clearance, CLcr=120 mL/min), urinary excretion dropped from 61% to 21% while AUC jumped by ~2-folds in critically ill patients with severe renal insufficiency (CLcr=20 mL/min). [27] This illustrates that neither total clearance nor renal excretion clearance is proportional to glomerular filtration rate because elimination is only partially renal and renal impairment may alter the free fraction and tubular reabsorption. Also, $t_{1/2}$ was ~19 h in patients with CLcr≤40 mL/min *vs* ~8 h in patients with CLcr≥80 mL/min. [80] In order to take into account this effect of renal impairment on daptomycin PK, it is recommended to administer daptomycin once every 48 h instead of once every 24 h for patients with CLcr lower than 30 mL/min. [48]

PK in patients with haemodialysis. PK of daptomycin in patients undergoing continuous renal replacement therapy (CRRT) have been described by several groups. [83-87] Daptomycin is excreted during CRRT, mean total clearances estimated during continuous veno-venous haemodialysis (CVVHD) varied between 0.68 and 1.03 L/h (corresponding to 11 and 17 mL/min).[83, 85, 88-91] Mean total clearances estimated during continuous veno-venous haemodiafiltration (CVVHDF) varied between 0.36 and 0.61 L/h.[83, 84, 86, 87] These values are quite close to the clearance values observed in healthy volunteers (0.56-

0.70 L/h). Based on these results, the authors performed simulations to determine the most appropriate dosing regimens to achieve the efficacy targets and to avoid muscle toxicity. It is important to note that the unbound fraction of daptomycin was twice higher in haemodialyzed critically ill patients compared with values reported in non-haemodialyzed patients (16-18% vs 9%). [27, 85, 86] Accordingly, as simulations performed in these studies were performed from total concentrations, actual unbound concentrations should have been underestimated as well as PTA to reach efficacy and toxicity targets. Dosing recommendations for patients undergoing CRRT are still a matter of debate. Thus, the dosages recommended by the various authors range from 6 mg/kg q48h to 8 mg/kg q24h. [83-91]

Clearance of daptomycin in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) was reported to be 0.31 L/h. [92] In that case, an IV administration of daptomycin 4 to 6 mg/kg q48h appears to be adequate to achieve effective plasma concentrations. [92]

Hepatic impairment. Results from an open label, single dose study (6 mg/kg) showed that moderate hepatic impairment (Child-Pugh B) did not affect daptomycin PK. [13] No data are available for severe hepatic impairment, therefore daptomycin should be used with caution for these patients. In addition, hepatic failure may be accompanied by hypoalbuminemia which may alter protein binding of daptomycin.

Obese. Regulatory agencies approved daptomycin dosing proportional to actual body weight (4 or 6 mg/kg/day depending on indication). When considering non-weight-normalized parameters, the volume of distribution [80, 93, 94] and the elimination clearance [87, 94] of daptomycin have been shown to increase with body weight. However, after administration of a weight-proportional dose of daptomycin, exposure (AUC, Cmax, Cmin) was 25% to 93% higher in obese subjects compared to non-obese subjects. [94-96] Moreover, complicated obese patients who received daptomycin dosed on actual body weight have increased rates of

CPK elevations. [97] Thus, dosing regimens, either fixed (500 mg/day), based on ideal body weight or based on adjusted body weight (calculated according to a function depending on actual and ideal body weights), have been proposed. [96, 98-100] Although it appears that the administration of fixed doses is most likely to lead to comparable exposures between obese and non-obese patients, this approach needs to be better evaluated and the determination of fixed doses to achieve effective exposure in obese patients remains to be done. [96] Furthermore, in order to make dose recommendations in obese patients, it seems important to measure the free fraction in this population.

Gender. In two studies, clearance has been shown to be 20-44% lower for female subjects than for male subjects. [56, 80, 81] However, in some other studies, difference of clearance between genders was not significant. [82, 101] It may be hypothesized that gender could be a better descriptor of the influence of body size on the clearance of daptomycin, but this requires further investigation.[56].

Paediatrics. After single administration of daptomycin 4 mg/kg, daptomycin clearance was about 20 mL/h/kg in children younger than 6 years and in young infants <12 months (compared to 8-10 mL/h/kg in healthy volunteers).[102-104] The systemic exposure in paediatric patients younger than 6 years was lower than in adolescents (12-17 years, CL~11 mL/h/kg) and adults (CL~8.3 mL/h/kg) for the same dose, due to decreased clearance with age. [48, 102] This results in under-exposure in children [102-104] and higher weight-based (*i.e.* mg/kg) doses of daptomycin may be required to achieve the efficacious exposures observed in adults. [105, 106] A single 8 or 10 mg/kg dose for children aged 2 to 6 years led to exposures comparable to those obtained in adults for a 4-6 mg/kg dose. [48, 107] Moreover, a report of two infants <2 months receiving 6 mg/kg daptomycin every 12 h concluded that this dosage was equivalent to adults treated with 4 mg/kg every 24 h. [108] Antachopoulos et al. even proposed that doses higher than 6mg/kg/12h should be used.[109]

However, it is known that protein binding of drugs may be decreased in children, and should therefore be evaluated for daptomycin in order to correctly interpret these results obtained for total concentrations. [110]

Elderly. An open-label, single-dose (4 mg/kg) Phase I study showed that total exposure ($AUC_{0-\infty}$) of daptomycin was 58% higher in geriatric subjects 75 years old compared with younger subjects between 18 and 30 years old.[111] The 35% lower clearance explaining this difference in exposure was in fact not due to the difference in age but to the difference in renal function. No statistical differences in Cmax and volume of distribution were observed between geriatric and younger subjects.

PK in critically ill patients. Intensive care unit (ICU) patients with infections often have other co-morbidities, such as renal failure, hypoalbuminemia, or obesity. In addition, the presence of sepsis may lead to acute renal failure and require haemodialysis. Therefore, they are at risk of having altered pharmacokinetics of daptomycin. As a matter of fact, pharmacokinetics of daptomycin is highly variable between ICU patients, but also highly variable for the same patient over time. [27, 30] Compared to healthy volunteers, one of the main differences observed in ICU patients is an increase by two folds on average of the volume of distribution, on average about twice as much (0.2 L/kg *vs* 0.1 L/kg). [25, 27, 30, 112] Reported clearances values are dependent on the renal function of patients included in the various clinical trials. [25, 27, 30, 112] In order to reach PK/PD targets for efficacy, it is generally recommended to give high, and off-label, doses of daptomycin (10 mg/kg/day or 560-840 mg/day) to ICU patients, except for those with reduced renal function, and to perform therapeutic drug monitoring. [25, 27, 30, 112] The pathophysiological state of ICU patients is rarely stable over time and this can affect the PK of daptomycin. For example, augmented renal clearance or the presence of sepsis may induce a decrease in daptomycin concentrations. [25, 113] The fact that the septic state of patients tends to improve over time has led some authors to

propose that the dosage of daptomycin should be adapted to the evolution of the pathology, in particular with high doses during the first days (10 mg/kg/day or 750 mg/day) then lower doses. [113] Overall, the unstable nature of the PK of daptomycin in ICU patients seems to be a strong argument for clinicians to use therapeutic drug monitoring for this patient population.

10 Therapeutic drug monitoring (TDM)

TDM of daptomycin is currently not widespread, but it could benefit some patients.[114, 115] Thus, some patients are at risk of having disturbed pharmacokinetics, such as ICU patients with sepsis, patients with renal or hepatic insufficiency, patients with augmented renal clearance, patients undergoing renal replacement therapy, obese patients, paediatric or geriatric patients, or patients with severe burns. In addition, in order to monitor the risk of toxicity, there is an interest in monitoring daptomycin concentrations for patients receiving high doses. [116]

Few (one to our knowledge) commercial kits are available for the determination of daptomycin, but HPLC-UV and LC-MS/MS assay methods have been published (see bioanalytical section). Some targets for efficacy and toxicity have been published. A target of AUC/MIC>666 may be selected for clinical efficacy, even if this value needs to be confirmed in larger patient cohorts. [30] In addition, protein binding, and thus possible hypoalbuminemia, should be taken into account when interpreting and comparing daptomycin assay results with this target value (*cf* protein binding section). A Cmin greater than 3.2 mg/L was also proposed as an efficacy target.[31] The target value for Cmin not to be exceeded in order to limit the risk of undesirable muscular effects is 24.3 mg/L. [2, 3, 34, 35]

Ideally, TDM of daptomycin should be based on free concentrations, which is technically difficult at the moment. It is therefore based on total concentrations. Monitoring for muscle toxicity is fairly simple, since it is sufficient to measure Cmin just before next administration.

On the other hand, monitoring of efficacy and estimation of AUC is more problematic and requires either the use of Bayesian approaches, or the use of simplified equations requiring measurements of one concentration approximately two hours after the start of the infusion and of Cmin. [117] As alternative approaches, some authors have proposed that Cmin should exceed 3.2 mg/L [31] or that Cmax at the end of the infusion should exceed 100 mg/L. [85, 118]

11 Conclusion

Due to a low level of resistance, daptomycin has an important place in the treatment of Gram-positive infections. Its pharmacokinetics is characterized by predominantly renal elimination and high protein binding (~90%). Due to high inter-individual variability, therapeutic monitoring of daptomycin concentrations may be of interest for certain patients such as ICU patients, patients with renal or hepatic insufficiency, dialysis patients, obese patients or children.

Compliance with Ethical Standards

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12 References

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