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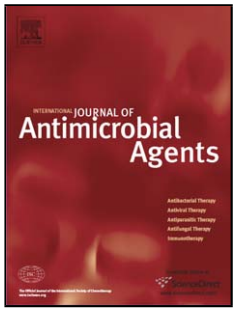

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Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of fosfomycin for the treatment of patients with systemic infections

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ABSTRACT

The advancing antimicrobial drug resistance in common bacterial pathogens, along with the relative shortage of new antibacterial agents, call for the re-evaluation of available therapeutic options. Fosfomycin is an established treatment option for uncomplicated urinary tract infections. Here we review and evaluate the main pharmacokinetic and pharmacodynamic parameters of intravenously administered fosfomycin with regard to its use for systemic infections. Fosfomycin is a relatively small, hydrophilic agent with almost negligible serum protein binding. It is excreted unchanged in urine, achieving high concentrations for a prolonged period. Fosfomycin has good distribution into tissues, achieving clinically relevant concentrations in sites such as serum, soft tissue, lungs, bone, cerebrospinal fluid and heart valves. Fosfomycin has shown antimicrobial activity against biofilms, particularly in combination with fluoroquinolones. It also exerts immunomodulatory effects, mainly on lymphocyte and neutrophil function. Potentially useful properties of fosfomycin regarding its use in combination regimens include reduction in the expression of certain penicillin-binding proteins and attenuation of nephrotoxicity caused by several antimicrobial agents. In conclusion, the pharmacokinetic and pharmacodynamic properties of fosfomycin do not preclude its use for various types of systemic infections and suggest further research on relevant clinical applications of this agent.

1. Introduction

There is relative shortage of antibiotics for the treatment of infections caused by bacterial pathogens with advanced antimicrobial drug resistance. Re-evaluation of the antimicrobial activity and clinical effectiveness of rather neglected antimicrobial agents against current 'problem' pathogens may provide an at least temporary solution to the abovementioned problem. Fosfomycin, originally isolated in 1969 as a product of *Streptomyces* spp. [1], could prove to be such an example. Several studies have shown that fosfomycin has retained substantial antimicrobial activity against 'problem' Gram-positive and Gram-negative pathogens, including meticillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Streptococcus pneumoniae* as well as extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae [2,3].

Fosfomycin administered orally as the tromethamine salt constitutes a well established therapeutic option for the treatment of acute uncomplicated cystitis [4]. Furthermore, intravenous (i.v.) fosfomycin has long been used clinically in certain countries for the treatment of infections other than those involving the urinary tract [5]. The cumulative clinical experience is generally favourable of the utility of fosfomycin for such indications. Here we review data regarding the pharmacokinetic and pharmacodynamic properties of fosfomycin with regard to its use in the treatment of various types of systemic infections.

2. Pharmacokinetic characteristics of fosfomycin

Fosfomycin, a phosphonic acid derivative (cis-1,2-epoxypropyl-phosphonic acid), is a relatively small molecule (molecular weight 138 Da) with hydrophilic properties.

Absorption of orally administered fosfomycin occurs in the small intestine through a saturable carrier-mediated process (possibly associated with the phosphate transport system) as well as a non-saturable process that exhibits first-order kinetics [6]. The degree of enteral absorption of the tromethamine salt of fosfomycin is higher compared with that of the calcium salt [7]. The latter has

relatively low oral bioavailability (12–28%) [8,9] as it is subject to inactivation by hydrolysis in the acidic gastric environment [10]. The oral bioavailability of the tromethamine salt of fosfomycin is ca. 40% [11]. Administration of fosfomycin tromethamine with food may reduce the degree of drug absorption [12].

The pharmacokinetic characteristics of orally administered fosfomycin tromethamine have previously been reviewed in detail [13]. In brief, following administration of a single dose of 3 g (ca. 50 mg/kg) of fosfomycin tromethamine (the usual oral dose), the maximum serum drug concentration (C_{max}) is ca. 22–32 mg/L, reached within 2–2.5 h. Fosfomycin has a serum elimination half-life ($t_{1/2}$)of ca. 2.4–7.3 h. The corresponding area under the concentration–time curve (AUC) is ca. 145–228 mg·h/L [13]. Data on the apparent volume of distribution (V_d) following oral administration of fosfomycin tromethamine are rather conflicting; values between 40 L and 136 L have been reported [7,14,15]. It should also be noted that the degree of protein binding of fosfomycin in serum is negligible.

Table 1 presents data on the pharmacokinetic parameters in serum as well as in various tissues or sites of parenterally administered fosfomycin, as reported in various relevant studies. To evaluate further the degree of penetration of fosfomycin into tissues, we calculated the ratio of the concentration or AUC of fosfomycin in different body sites to the corresponding value in serum, using relevant data provided by individual studies. Thus, according to the data presented in Table 1, the degree of penetration of fosfomycin into tissues appears to be greater for subcutaneous tissue and muscle tissue, followed by lung and bone tissue.

Elimination of fosfomycin from the human body takes place almost exclusively through renal clearance, specifically glomerular filtration. No metabolic by-products of fosfomycin have been identified [13].

3. Pharmacodynamic characteristics of fosfomycin

Fosfomycin exerts bactericidal antimicrobial activity against susceptible pathogens by blocking the early stage of bacterial cell wall synthesis [36]. Specifically, fosfomycin binds to and inhibits the cytoplasmic enzyme uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc) enolpyruvyl transferase (MurA). This enzyme is responsible for the synthesis of UDP-*N*-acetylenolpyruvylglucosamine, which is a metabolic pentapeptide intermediate in the biosynthesis of the peptidoglycan layer of the bacterial cell wall [37]. To exert its action, fosfomycin needs to penetrate the bacterial cell membrane. This is accomplished by means of two distinct membrane uptake systems, namely the L-α-glycerophosphate and the hexose phosphate systems. Of note, the activity of the latter system is induced by glucose-6-phosphate.

Whether fosfomycin exhibits concentration-dependent or time-dependent bactericidal activity has not been accurately established. In this respect, some studies have found that fosfomycin demonstrates concentration-dependent killing activity against strains of *Escherichia coli* and *Proteus mirabilis* in vitro as well as strains of *S. pneumoniae* in vivo [38,39]. However, other studies have noted time-dependent bactericidal activity of fosfomycin against *S. aureus* strains in vitro [32,40].

Fosfomycin has also exhibited a rather prolonged post-antibiotic effect (PAE) in vitro against strains of *E. coli* and *P. mirabilis*, varying between 3.4 h and 4.7 h depending on the drug concentration applied [38]. However, against strains of *S. aureus* a relatively shorter PAE has been observed (0.5–1.4 h) [41].

4. Specific therapeutic considerations

4.1. Fosfomycin use in specific patient groups

The presence of renal insufficiency affects the pharmacokinetics of fosfomycin. Specifically, oral administration of 25 mg/kg fosfomycin tromethamine in patients with various degrees of renal insufficiency has resulted in higher serum C_{max} and AUC compared with healthy controls [42]. In

addition, the $t_{1/2}$ of fosfomycin in serum has been shown to correlate positively with the creatinine clearance rate [18]. Fosfomycin is also actively removed through haemodialysis; administration of the drug after the dialysis session results in maintenance of adequate serum concentrations between sessions [23]. Finally, in critically ill patients undergoing continuous venovenous haemofiltration, no adjustment in fosfomycin dosage is necessary [33].

Furthermore, the presence of hepatic insufficiency does not necessitate any adjustments in fosfomycin dosage. With regard to pregnancy, the use of fosfomycin is not contraindicated (pregnancy category B), although it is known to cross the placenta. Data on human use of fosfomycin during lactation are lacking.

In elderly individuals, a significant increase in the fosfomycin serum AUC, along with a reduction in renal clearance and the amount of drug excreted in urine in 24 h, has been observed in comparison with younger individuals [7]. However, no significant difference was noted in the serum C_{max}, time to serum C_{max} and V_d between the above two groups.

4.2. Urinary tract infections (UTIs)

Fosfomycin tromethamine used in a single 3 g oral dose has been a well established therapy for uncomplicated UTIs. This can partly be attributed to the favourable pharmacokinetic properties of fosfomycin in this compartment. Specifically, peak fosfomycin concentrations in urine of 1053–4415 mg/L are achieved within 4 h after administration of the usual 3 g single dose, whilst concentrations of >128 mg/L can persist for 48 h [13]. The amount of fosfomycin excreted in urine during the first 4 h after administration of a 1 g dose represents a small portion of the total drug quantity (17%) [14]. Substantially high drug concentrations (above the usual minimum inhibitory concentrations of common uropathogens) may also persist in the bladder mucosa for at least 36 h [43]. Furthermore, fosfomycin appears to reduce the ability of bacteria to adhere to urinary epithelial cells [44].

The effectiveness of the fosfomycin tromethamine 3 g single-dose regimen for the treatment of acute uncomplicated lower UTIs has been evaluated in a number of comparative clinical trials. Fosfomycin therapy has not been found to be inferior in terms of clinical or microbiological effectiveness to 7-day pipemidic acid [45,46], 5-day amoxicillin/clavulanic acid [47]. 5-day trimethoprim/sulfamethoxazole [48], 7-day norfloxacin [49,50], 5-day cefalexin [51] or 7-day nitrofurantoin therapy [52].

In a small trial with an open-label design, fosfomycin has been compared with ampicillin for the treatment of acute pyelonephritis [25]. A total of 38 patients were treated either with i.v. fosfomycin (8 g twice daily) or ampicillin (2 g thrice daily) for 1 week each. The clinical success rates were 44% and 28%, respectively ($P > 0.2$).

Oral fosfomycin tromethamine has also been evaluated as chemoprophylaxis for transurethral prostatectomy [53]. In this respect, administration of 3 g of fosfomycin tromethamine both before and after the procedure appears to be effective and safe in reducing post-operative bacteriuria.

4.3. Respiratory tract infections

Several studies have described the penetration of fosfomycin into sites of the lower respiratory tract. Parenteral administration of 2 g of fosfomycin prior to pulmonary operations has resulted in concentrations of 12–16 mg/L in healthy lung tissue, with corresponding serum concentrations of 32 mg/L. Concentrations of the drug in tumorous lung tissue were approximately one-half of those reported in healthy tissue [16]. Furthermore, i.v. administration of 4 g of fosfomycin in patients with tracheostomy has resulted in a peak drug concentration in bronchial secretions of 13.1 mg/L, whilst concentrations obtained 2 h after administration of fosfomycin corresponded to 13% of the serum levels [17]. In addition, i.v. administration of 30 mg/kg fosfomycin to patients with transudative pleural effusion has resulted in peak drug concentrations of 42.6 mg/L [22].

A randomised controlled trial has compared the effectiveness of i.v. fosfomycin [4 g every 8 h (q8)] versus gentamicin (80 mg q8h), both combined with ampicillin [54]. Relatively high clinical success rates were observed in both treatment groups (94% vs. 80% for 17 and 15 patients, respectively).

4.4. Central nervous system (CNS) infections

Despite being a relatively hydrophilic agent, fosfomycin has the ability to cross the blood–brain barrier to a clinically relevant degree. In patients with cerebrospinal fluid (CSF) drainage, the CSF concentration of fosfomycin was 9.2% and 13.8% of the corresponding concentration in serum after a 5 g and 10 g i.v. dose, respectively [24]. Furthermore, in patients who received 5 g of fosfomycin three times daily, drug levels of >30 mg/L were reached in the CSF by the second day of treatment. The presence of meningeal inflammation was associated with an increase in fosfomycin CSF concentration by ca. three-fold [24]. In patients with ventriculostomy-associated ventriculitis who received 8 g of i.v. fosfomycin three times daily, the CSF-to-serum fosfomycin AUC ratio has been found to be 27% at steady state [32]. Fosfomycin has also been shown to achieve clinically relevant drug concentrations in the brain parenchyma [29].

It should be mentioned that fosfomycin has been used clinically for the treatment of CNS infections, mainly caused by *S. pneumoniae*, *Neisseria meningitidis* and *S. aureus*, administered in combination with cephalosporins [55,56], penicillin G or ampicillin [57], aminoglycosides [58] or even as a single antibiotic agent [59].

4.5. Soft tissue infections

Several studies have evaluated the degree of penetration of fosfomycin into soft tissue (muscle or subcutaneous tissue) [28,30,31,60]. Briefly, i.v. administration of 4 g and 8 g of fosfomycin to healthy volunteers resulted in muscle and subcutaneous tissue fosfomycin $AUC_{0–8h}$ values that were ca. 50% and 70%, respectively, of the corresponding serum values [28]. Similar findings have been observed

in additional studies evaluating the degree of penetration of fosfomycin into soft tissue in patients with sepsis, cellulitis or diabetic foot infections [30,31,60].

There are also clinical data that further support the use of fosfomycin in the treatment of soft tissue infections. A multicentre study has evaluated treatment with fosfomycin (8–24 g daily) in combination with a conventional agent for patients with limb-threatening diabetic foot infections. Limb preservation was achieved in the great majority (48 of 52) of patients [61].

4.6. Abscesses

Fosfomycin has demonstrated an increase in bactericidal activity in vitro under anaerobic conditions, which might be clinically relevant for the treatment of chronic suppurative infections and abscesses [62]. Penetration of fosfomycin into purulent collections does not appear to relate to serum drug concentration but rather to morphological characteristics of lesions, including the permeability of the outer wall and the vascularity of surrounding tissue [34]. The half-life of fosfomycin in such lesions is high but is also variable.

4.7. Intra-abdominal infections

The distribution of fosfomycin in intra-abdominal sites has not been well studied. Available relevant data suggest that fosfomycin attains clinically relevant concentrations in several intra-abdominal sites, such as gall bladder fluid and the gall bladder wall as well as purulent ascitic fluid and the appendix [63]. Of note, fosfomycin has been effectively evaluated as an agent for antibiotic prophylaxis in upper gastrointestinal, hepatobiliary or colorectal surgery in comparison with other agents [64–66].

4.8. Bone infections

Penetration of fosfomycin into bone tissue has been evaluated in patients given 4 g of fosfomycin intravenously as prophylaxis for total hip replacement surgery [19,20]. A linear correlation between

the concentration of fosfomycin in serum and bone tissue was observed. The peak concentrations of fosfomycin in cancellous and cortical bone tissue did not appreciably differ. In addition, penetration of fosfomycin into chronically infected bone tissue was higher compared with non-infected bone tissue [67]. Fosfomycin achieved clinically relevant concentrations in cortical bone, cancellous bone and post-osteomyelitis sequestra. A recent study on the penetration of fosfomycin in the bone tissue of patients with deep-seated bacterial foot infections showed that a 100 mg/kg dose achieves therapeutic levels in bone tissue well above the expected MICs of common pathogens for a rather prolonged period of time [35]. Of note, the structural similarity between the fosfomycin molecule and that of hydroxyapatite could facilitate the accumulation of fosfomycin in bone tissue [68].

There is considerable clinical experience regarding the use of fosfomycin, mainly in combination regimens, for various types of bone infections [69], primarily complicated bone fractures [70] and osteomyelitis or septic arthritis in children [71,72]. It is noteworthy that a recent survey among paediatricians and paediatric orthopaedists in France found that the combination of fosfomycin with a third-generation cephalosporin was one of the most popular therapeutic options for acute osteomyelitis in children [73].

4.9. Bloodstream infections

One study has evaluated the pharmacokinetics of intravenously administered fosfomycin (50 mg/kg three to four times daily) in combination with cefotaxime for the treatment of three cases of *S. aureus* or *Staphylococcus epidermidis* septicaemia [74]. The mean serum concentration of fosfomycin obtained 15 min after administration was 81.8 mg/L, whilst the mean trough concentration was 23.5 mg/L.

The concentration of fosfomycin has also been measured in cardiac valve tissue following peri-operative administration to patients undergoing open heart surgery for valvular heart disease. Peak tissue concentrations achieved in cardiac valves varied between 27.1 mg/L and 76.9 mg/L for aortic valves and 39.6 mg/L and 69.4 mg/L for mitral valves [26].

The relatively good tissue penetration of fosfomycin in heart and other tissues has been found to be clinically relevant in a study evaluating the use of a fosfomycin/pefloxacin combination regimen as antibiotic prophylaxis for open heart surgery [75]. It should also be noted that in certain countries fosfomycin has been used clinically in combination with vancomycin for the treatment of endocarditis due to MRSA [76].

4.10. Biofilm-associated infections

Recent research has shown that fosfomycin, used in combination with a fluoroquinolone, has good in vitro antimicrobial activity against *Pseudomonas aeruginosa* biofilms [77–80]. This finding has been related to the ability of fosfomycin to penetrate into deep layers of newly formed or even mature biofilms along with enhancement of its antimicrobial activity under anaerobic conditions [79,80]. The antimicrobial activity of fosfomycin in biofilms may be of particular clinical importance for the treatment of episodes of pulmonary exacerbation of cystic fibrosis, as has been shown in various relevant studies [81–83].

4.11. Immunomodulatory effects of fosfomycin

Fosfomycin may have several modulatory effects on immune system function. Regarding the adaptive immune system, fosfomycin has been shown to inhibit in vitro the activation of human B- and T-lymphocytes [84,85]. Fosfomycin is also thought to decrease the production of pro-inflammatory cytokines [such as interleukin (IL)-1α, IL-1β, tumour necrosis factor-alpha (TNFα) and IL-8) and increase the production of other cytokines (IL-6 and IL-10) [86,87]. In vivo data suggest that the above properties of fosfomycin could confer protection against sepsis-induced organ dysfunction [88]. However, the clinical relevance of these findings has not been clarified [89].

Regarding the innate immune system, fosfomycin has demonstrated variable effects on neutrophil function [90]. Fosfomycin may increase the susceptibility of certain bacteria to phagocytosis [91] and

particularly enhance the bactericidal function of neutrophils exhibiting intraphagocytic antibacterial activity. The latter effect of fosfomycin has been demonstrated on neutrophils derived from immunocompromised patients [92,93].

4.12. Use of fosfomycin in combination drug regimens

There are laboratory findings suggesting that fosfomycin modifies the production of penicillin-binding proteins (PBPs) in different bacterial species [94,95]. This property of fosfomycin could be useful to overcome β-lactam resistance associated with production of PBPs with reduced affinity for β-lactams, as observed in penicillin-resistant *S. pneumoniae* and MRSA.

Fosfomycin has been found in vivo to mitigate the toxicity of various co-administered antibiotics, for example nephrotoxicity related to aminoglycosides [96], glycopeptides [97] or amphotericin B [98] as well as ototoxicity related to aminoglycosides [99] or polymyxin B [100].

4.13. Toxicity of fosfomycin

The most common adverse events of orally administered fosfomycin tromethamine are typically of mild severity and include mainly gastrointestinal irritation (1–9%), vaginitis (6%), headache and dizziness (1–4%) [13]. Serious adverse events such as anaphylactic shock, angioedema, aplastic anaemia, asthma exacerbation, cholestatic jaundice, liver necrosis, toxic megacolon and optic neuritis have been rarely noted in post-marketing surveillance reports [15,101]. The most common adverse events of intravenously administered fosfomycin, as reported in the literature [5], include gastrointestinal disturbance and local phlebitis; in general, they are well tolerated and do not necessitate treatment discontinuation. Severe toxicity of i.v. fosfomycin has also been described [102], although rarely. The favourable safety profile of fosfomycin presumably allows for the administration of relatively high doses of the drug, which could increase the likelihood of attainment of pharmacodynamic targets while treating systemic infections. High levels of fosfomycin might additionally reduce the likelihood of emergence of resistance during therapy with fosfomycin [103].

5. Conclusion

Evaluation of the available evidence on the pharmacokinetic and pharmacodynamic properties of fosfomycin does not preclude its use in various types of systemic infections. Specifically, fosfomycin is a relatively small, hydrophilic molecule with negligible serum protein binding. Intravenous administration of various doses of fosfomycin has resulted in attainment of clinically relevant concentrations in various sites such as serum, soft tissue, bone, lung, CSF and heart valves. Additional pharmacodynamic properties of fosfomycin, such as good penetration and antimicrobial activity against biofilms, as well as modulatory effects in various parameters of immune system function might also be of clinical relevance. The aforementioned data support further research on the antimicrobial activity and clinical utility of fosfomycin for the treatment of systemic infections caused by contemporary resistant pathogens.

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Table 1

Data from selected studies on the pharmacokinetic parameters of parenterally administered fosfomycin, including penetration into various sites

Reference	Study subjects, age [a], gender	Fosfomycin dose	V_d [b]	$t_{1/2}$ (h) [b]	Systemic clearance [b]	Site or tissue	Serum concentration (mg/L) [b]	Site concentration (mg/L) [b]	Site:serum concentration ratio [c]	Serum AUC (mg·h/L) [b]	Site AUC (mg·h/L) [b]	Site:serum AUC ratio [c]
Goto et al., 1981 [9]	7 healthy volunteers, 36.3 ± 12.3 years, all M	20 mg/kg i.v. infusion lasting 5 min	0.32 ± 0.08 L/kg	2.25 ± 0.74	2.08 ± 0.45 mL/min/kg	NR	C_{max}: 132.1 ± 31.8	NA	NA	0–∞: 167.9 ± 26.4	NA	NA
		40 mg/kg i.v. infusion lasting 5 min	0.36 ± 0.06 L/kg	2.22 ± 0.46	2.31 ± 0.22 mL/min/kg		C_{max}: 259.3 ± 32.5			0–∞: 290.8 ± 25.3		
Farago et al., 1980 [16]	12 patients undergoing pulmonary operations, 42–73 years, 10 M/2 F	2 g i.m.	NR	NR	NR	Lung (normal tissue)	$C_{70–100min}$: 27.9 ± 9.5; $C_{105–120min}$: 37.6 ± 4.5	$C_{70–100min}$: 12 ± 2.4; $C_{105–120min}$: 13 ± 1.2	70–100 min: 0.43; 105–120 min: 0.35	NR	NR	NA
						Lung (tumorous tissue)		$C_{70–100min}$: 6.4; $C_{105–120min}$: 6.9	70–100 min: 0.23; 105–120 min: 0.18	NR	NR	NA
	14 patients undergoing pulmonary operations, 50–80 years, 11 M/3 F	2 g i.v.	NR	NR	NR	Lung (normal tissue)	$C_{50–75min}$: 39.59 ± 3.9 $C_{80–110min}$: 31.3 ± 1.5	$C_{50–75min}$: 12.6 ± 1.3 $C_{80–110min}$: 16.2 ± 2.1	50–75 min: 0.32 80–110 min: 0.52	NR	NR	NA
Berthelot et al., 1983 [17]	11 patients with tracheostomy, 24–80 years, NR	4 g i.v. infusion at a rate of 1 g/h (measurement performed post infusion)	NR	NR	NR	Bronchial secretions	C_{max}: 120 ± 36; C_{2h}: 52.5 ± 18.22	C_{30min}: 13.1 ± 11.37; $C_{2h:}$ 7 ± 7.14	2 h: 0.13	NR	NR	NA
Fernandez Lastra et al., 1983 [18]	9 patients with normal renal function, 30 ± 11.7 years; NR	30 mg/kg i.v. bolus	21.2 ± 10.4 L	1.91 ± 0.5	131 ± 52.8 mL/min	Interstitial fluid (obtained from vacuum-induced skin blisters)	C_{max}: 644	C_{max}: 50.5 ± 16.3	0.08	NR	NR	NA
	8 patients with renal impairment, 44.5 ± 15.6 years, 6 M/2 F		17.8 ± 6.8 L	16.3 ± 11.9	18 ± 13.8 mL/min		NA	C_{max}: 69.3 ± 39.5	NA	NR	NR	NA
Sirot et al., 1983 [19]	20 patients undergoing total hip replacement, 35–80 years, 13 M/7	4 g i.v. infusion at a rate of 1 g/h	NR	NR	NR	Cancellous bone	C_{1h}: 105 ± 12.4; C_{3h}: 67.8 ± 15.9	C_{1h}: 19.6 ± 4.8; C_{3h}: 10 ± 4.2	1 h: 0.19 ± 0.04; 3 h: 0.15 ± 0.04	NR	NR	NA

	F					Cortical bone		C_{1h}: 13.3 ± 3.7; C_{3h}: 8.2 ± 3.6	1 h: 0.13 ± 0.04; 3 h: 0.13 ± 0.05		NR	NA
Quentin et al., 1983 [20]	20 patients undergoing total hip replacement, 67.7 ± 10.1 years, 8 M/12 F	4 g i.v. infusion at a rate of 1 g/h	NR	NR	NR	Cancellous bone Cortical bone	$C_{1–2h}$: 77.7 ± 20	$C_{1–2h}$: 18 ± 14.8 $C_{1–2h}$: 17.2 ± 12.5	0.24 ± 0.19 0.23 ± 0.16	NR	NR NR	NA NA
Fernandez Lastra et al., 1984 [21]	10 patients with end-stage renal impairment under haemofiltration, 33–63 years, 7 M/3 F	30 mg/kg i.v. bolus given before haemofiltration session	NR	4.04 ± 1.77	91.94 ± 23.04 mL/min	NR	C_{max}: 186.56 ± 110.99	NA	NA	NR	NR	NA
Lastra et al., 1984 [22]	6 patients with transudative pleural effusion, 54–85 years, 5 M/1 F	30 mg/kg i.v. bolus	16.79 ± 8.39 L	3.27 ± 1.25	63.37 ± 11.18 mL/min	Pleural fluid	C_{max}: 350.2 ± 124.69	C_{max}: 42.63 ± 16.02	0.12	0–∞: 485.47 ± 38.14	NR	0.95
Bouchet et al., 1985 [23]	6 patients undergoing haemodialysis, NR, NR	2 g i.v. given 15 min before haemodialysis session	23.6 ± 7.4 L	4.16 ± 0.69	64.66 ± 17.37 mL/min	NR	C_{4h}: 32.28 ± 8.97	NR	NA	0–∞: 540.16 ± 131.79	NR	NA
	6 patients undergoing haemodialysis, NR, NR	2 g i.v. given after haemodialysis session	NR	48.8 ± 17.54	NR		C_{44h}: 62.16 ± 32.34			0–∞: 9021.8 ± 5060.88		
Kuhnen et al., 1987 [24]	35 patients with intraoperative or therapeutic CSF drainage	5 g i.v. bolus	18.5 L	2	118.8 mL/min	CSF	C_{max}: 260.1 ± 105.7	C_{max}: 11.6	0.04	0–∞: 420.95	0–∞: 38.89	0.09
	5 patients with intraoperative or therapeutic CSF drainage	10 g i.v. bolus	24.9 L	NR	NR		C_{max}: 440	C_{max}: 17.7	0.04	0–∞: 423.57	0–∞: 58.49	0.14
Ode et al., 1988 [25]	10 patients with pyelonephritis, NR, NR	8 g i.v. twice a day (measurement at steady state)	18.9 ± 5.7 L	2.3 ± 0.3	NR	Kidney	C_{max}: 394.7 ± 141.2	C_{max}: 84.7 ± 47.9	0.22	0–12h: 1763 ± 700	0–12h: 611 ± 364	0.35
Hirt et al.,	36 patients undergoing	5 g i.v. infusion lasting	NR	NR	NR	Aortic valve	C_{max}: 203.7 ±	C_{max}: 27.1–76.9	0.13–0.38	NR	NR	NA

1990 [26]	open heart surgery, 69.1 ± 9.1 years, 21 M/15 F	30 min	NR	NR	NR	Mitral valve	44.7	C_{max}: 39.6–69.4	0.19–0.34			NA
Forestier et al., 1996 [27]	21 patients undergoing cataract surgery, 68.95 ± 21.1 years, 5 M/16 F	4 g i.v. infusion lasting 60 min	13.38 L	2.98	NR	Aqueous humour	C_{max}: 252.45 ± 96.22	C_{max}: 14.63 ± 5.54	0.06	0–∞: 703.75	0–∞: 146.45	0.2
Frossard et al., 2000 [28]	6 healthy volunteers, 23–29 years, all M	4 g i.v. infusion lasting 60 min	NR	NR	NR	Muscle	C_{max}: 202 ± 20	C_{max}: 97 ± 13	0.48	0–8h: 443.2 ± 41.36	0–8h: 460.73 ± 40.05	0.48 ± 0.08
						Subcutaneous tissue		C_{max}: 144 ± 19	0.71		0-8h: 597.03 ± 48.62	0.74 ± 0.12
		8 g i.v. infusion lasting 60 min	NR	NR	NR	Muscle	C_{max}: 395 ±46	C_{max}: 156 ± 16	0.39	0–8h: 886.65 ± 70.75	0–8h: 201.88 ± 57.07	0.53 ± 0.04
						Subcutaneous tissue		C_{max}: 208 ± 30	0.53		0-8h: 313.97 ± 44.02	0.71 ± 0.11
Brunner et al., 2002 [29]	2 patients requiring neurosurgical ICU treatment, 22 years and 28 years, 1 M/1 F	4 g i.v. bolus	NR	NR	NR	Brain parenchyma	C_{max}: 606 and 244 [d]	C_{max}: 42 and 12 [d]	0.07 and 0.05 [d]	NR	NR	0–∞: 0.21 and 0.08 [d]
Joukhadar et al., 2003 [30]	9 patients with sepsis, 67 ± 3 years, NR	8 g i.v. infusion lasting 20 min	31.5 ± 4.5 L	3.9 ± 0.9	120 ± 21.7 mL/min	Muscle tissue	C_{max}: 357 ± 28	C_{max}: 247 ± 38	0.69	0–4h: 721 ± 66	0–4h: 501 ± 69	0.70 ± 0.07
Legat et al., 2003 [31]	6 patients with severe uncomplicated cellulitis, 61.7 ± 3.9 years, 3 M/3 F	200 mg/kg i.v. infusion lasting 30 min divided into three daily doses (measurement at steady state)	NR	NR	NR	Subcutaneous tissue, non-inflamed	C_{max}: 344 ± 53.6	C_{max}: 141 ± 68.6	0.41	0–8h: 1050 ± 139	0–8h: 742 ± 483	0.62 ± 0.22
						Subcutaneous tissue, inflamed		C_{max}: 150 ± 70.6	0.44		0–8h: 757 ± 492	0.71 ± 0.27
	6 patients with diabetic foot infections 62.5 ± 7.1 years, 3 M/3 F		NR	NR	NR	Subcutaneous tissue, non-inflamed	C_{max}: 320 ± 67.4	C_{max}: 136 ± 106.6	0.43	0–8h: 1331 ± 429	0–8h: 937 ± 848	0.73 ± 0.61
						Subcutaneous tissue, inflamed		C_{max}: 139 ± 76.7	0.43		0–8h: 782 ± 524	0.62 ± 0.35

Pfausler et al., 2004 [32]	6 patients requiring extraventricular drainage due to obstructive hydrocephalus, 53 ± 8 years, 4 M/2 F	8 g i.v. infusion lasting 30 min	30.8 ± 10.2 L	3 ± 1	123.3 ± 38.3 mL/min	CSF	C_{max}: 260 ± 85	C_{max}: 43 ± 20	0.17	0–8h: 929 ± 280	0–8h: 225 ± 131	0.23 ± 0.07
		8 g i.v. infusion lasting 30 min three times daily (measurement at steady state)	26.3 ± 9.7 L	4 ± 0.5	83.3 ± 33.3 mL/min		C_{max}: 307 ± 101	C_{max}: 62 ± 38	0.20	0–8h: 1035 ± 383	0–8h: 295 ± 179	0.27 ± 0.08
Gattringer et al., 2006 [33]	12 anuric ICU patients undergoing venovenous haemofiltration, 68 ± 8 years, 10 M/2 F	8 g i.v. infusion lasting 30 min	33.7 ± 12.7 L	12.1 ± 5.2	106.7 ± 126.7 mL/min	NR	C_{max}: 442.8 ± 124	NR	NA	0–12h: 2159.4 ± 609.8	NR	NA
Sauermann et al., 2005 [34]	11 patients with abscesses requiring surgical treatment, 50 ± 16 years, NR	8 g i.v. infusion lasting 30 min	28.6 ± 9.9 L	3.7 ± 2.2	126 ± 68 mL/min	Abscess fluid	C_{max}: 446 ± 128	C_{max}: 64 ± 67	NA	0–∞: 1330 ± 609	0–∞: 64±67	NA
Schintler et al., 2009 [35]	9 diabetic patients with deep-seated bacterial foot infections, 48–83 years, 6 M/3 F	100 mg/kg i.v. infusion lasting 30 min	NR	3.6 ± 1.2	NR	Subcutaneous tissue	C_{max}: 377.3 ± 73.2	C_{max}: 185.1 ± 34.2	0.49	0–6h: 785.1 ± 107.2	0–6h: 592.7 ± 77.5	0.76 ± 0.05
						Bone tissue		C_{max}: 96.4 ± 14.5	0.26		0–6h: 330.0 ± 55.3	0.43 ± 0.04

V_d, volume of distribution; $t_{1/2}$, half-life; AUC, area under the concentration–time curve; M, male; F, female; i.v., intravenous; i.m., intramuscular; NR, not reported; NA: not available; C_{max}, maximum concentration; C_{xh} or C_{xmin}, concentration measured at *x* h or min, respectively; CSF, cerebrospinal fluid; ICU, Intensive Care Unit.

[a] Presented as mean ± standard deviation or median (range), as available.

[b] Presented as mean ± standard deviation.

[c] Unless original relevant data were provided by the study authors, site-to-serum ratios were calculated by dividing the respective mean values.

[d] Actual values in each of the two patients.