European Journal of Drug Metabolism and Pharmacokinetics
https://doi.org/10.1007/s13318-022-00789-2

SHORT COMMUNICATION

Tigecycline Soft Tissue Penetration in Obese and Non-obese Surgical Patients Determined by Using In Vivo Microdialysis

Christoph Dorn[1] · David Petroff[2,3] · Alexander Kratzer[4] · Frieder Kees[5] · Charlotte Kloft[6] · Markus Zeitlinger[7] · Hermann Wrigge[3,8,9] · Philipp Simon[3,10]

Accepted: 17 July 2022
© The Author(s) 2022

Abstract

Background and Objective Tigecycline, a broad-spectrum glycylcycline antibiotic, is approved for use at a fixed dose irrespective of body weight. However, its pharmacokinetics may be altered in obesity, which would impact on the antibiotic's effectiveness. The objective of this study was to investigate the plasma and subcutaneous tissue concentrations of tigecycline in obese patients compared with those in a non-obese control group.

Methods Fifteen obese patients (one class II and 14 class III) undergoing bariatric surgery and 15 non-obese patients undergoing intra-abdominal surgery (mainly tumour resection) received a single dose of 50 or 100 mg tigecycline as an intravenous short infusion. Tigecycline concentrations were measured up to 8 h after dosing in plasma (total concentration), in ultrafiltrate of plasma (free concentration), and in microdialysate from subcutaneous tissue, respectively.

Results In obese patients, total peak plasma concentration (1.31 ± 0.50 vs 2.27 ± 1.40 mg/L) and the area under the concentration–time curve from 0 to 8 h ($AUC_{8h,plasma}$: 2.15 ± 0.42 vs 2.74 ± 0.73 h·mg/L), as normalized to a 100 mg dose, were significantly lower compared with those of non-obese patients. No significant differences were observed regarding the free plasma concentration, as determined by ultrafiltration, or the corresponding AUC_{8h} ($fAUC_{8h,plasma}$). Concentrations in interstitial fluid (ISF) of subcutaneous tissue were lower than the free plasma concentrations in both groups, and they were lower in obese compared to non-obese patients: the AUC_{8h} in ISF ($AUC_{8h,ISF}$) was 0.51 ± 0.22 h·mg/L in obese and 0.79 ± 0.23 h·mg/L in non-obese patients, resulting in a relative tissue drug exposure ($AUC_{8h,ISF}/fAUC_{8h,plasma}$) of 0.38 ± 0.19 and 0.63 ± 0.24, respectively.

Conclusion Following a single dose of tigecycline, concentrations in the ISF of subcutaneous adipose tissue are decreased in heavily obese subjects, calling for an increased loading dose.

EU Clinical Trials Registration Number EudraCT No. 2012-004383-22.

Key Points

After a single dose of tigecycline, total plasma concentrations were lower in obese compared to non-obese surgical patients.

Free plasma concentrations were similar in both groups.

Concentrations in interstitial fluid of subcutaneous tissue were lower than free plasma concentrations, and were lower in obese compared to non-obese patients.

✉ Christoph Dorn
christoph.dorn@ur.de

Extended author information available on the last page of the article

Published online: 09 August 2022

1 Introduction

With the rise in obesity worldwide, clinicians encounter obese patients with increasing frequency in their daily practice. Obesity may cause a number of pharmacokinetic changes, including an increase in the volume of distribution and changes in clearance [1, 2]. Although a reduced effectiveness of certain antibiotics for skin and skin-structure infections in severe obesity has been documented, especially after abdominal surgery, specific dosing recommendations for patients with obesity are often lacking on the product label [3].

Tigecycline is a broad-spectrum antibiotic that is approved for the treatment of complicated skin and skin-structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia. The approved standard dosing regimen of tigecycline is a 100-mg loading dose, followed by 50 mg twice daily irrespective of body weight. The pharmacokinetics of tigecycline are characterized by a large volume of distribution, between 7 and 10 L/kg, indicating extensive tissue penetration, and a long terminal half-life of approximately 40 h [4]. After intravenous short infusion (30 min) of a single dose of 100 mg tigecycline, a peak plasma concentration (C_{max}) of 1.45 ± 0.32 mg/L is typical, and the area under the concentration–time curve (AUC) is 5.19 ± 1.87 h·mg/L [5]. Concentrations of tigecycline in tissue homogenates of gall bladder, colon, and lung can be many times higher than concomitant plasma concentrations after a single dose, whereas the concentrations in synovial fluid or cerebrospinal fluid are lower than in plasma [6]. Concentrations equalling the free plasma concentrations were observed in subcutaneous interstitial fluid (ISF) of patients with diabetes after multiple dosing [7]. In that study, three of eight patients had a body mass index (BMI) of at least 30 kg/m^2, with a single class III obese individual (BMI of 41 kg/m^2) who had a significantly lower tissue penetration ratio compared with the remaining group [7, 8]. This may indicate impaired tissue penetration of tigecycline in heavily obese subjects, despite similar plasma pharmacokinetics [9]. In line with this assumption, a higher dose than the standard dose of 50 mg tigecycline b.i.d. has been suggested, especially for patients with high BMI, based on a retrospective clinical study in ICU patients. Of note, the authors regretted the lack of tissue level measurement in that study to support their recommendation [10]. Until now, the impact of obesity on the penetration of tigecycline into the ISF of subcutaneous tissue, a main site of bacterial infection, has not been investigated.

The objective of this study was to assess the penetration of tigecycline into the ISF of subcutaneous adipose tissue using microdialysis in obese and non-obese patients following a single dose of tigecycline as part of perioperative antibiotic prophylaxis.

2 Patients and Methods

2.1 Study Design

This prospective pharmacokinetic clinical trial was conducted at the Leipzig University Hospital as part of a larger pharmacokinetic study (EudraCT no. 2012-004383-22). Obese patients undergoing bariatric surgery and non-obese patients undergoing elective intra-abdominal surgery were eligible. Prior written informed consent was obtained from all study participants. Approval for the trial was obtained from the Leipzig University ethics committee (121/13-ff) and the Federal Institute for Drugs and Medical Devices of Germany (BfArM). The study protocol has been described previously [11]. Patients were to be given a single dose of 100 mg tigecycline (Pfizer, Berlin, Germany) as a 30-min intravenous infusion 60–30 min prior to incision. Venous blood samples were collected predose and after 0.5 h (end of infusion), 1, 2, 3, 4, 5, 6, and 8 h. Microdialysate probes (CMA 63 microdialysis probe, cutoff 20,000 Da, CMA, Kista, Sweden) were inserted subcutaneously in both upper arms and perfused with 2 µL/min saline. Microdialysate was collected predose (baseline) and at 0.5-h intervals up to 2 h, followed by 1-h intervals up to 8 h. After the sampling period, the probes were calibrated using the "retrodialysis-by-drug" method with tigecycline 500 mg/L in saline [12]. The primary endpoint was defined as the AUC from 0 to 8 h of the subcutaneous ISF concentration ($AUC_{8h,ISF}$) in the obese group compared with the non-obese group. As a secondary endpoint, the relative tissue distribution, i.e. the ratio of $AUC_{8h,ISF}$ to the AUC_{8h} of the free plasma concentration ($AUC_{8h,ISF}/fAUC_{8h,plasma}$), was determined.

2.2 Drug Assay and Pharmacokinetic and Statistical Analysis

The concentrations of tigecycline were determined by HPLC with photometric detection, as described previously [13]. The assay was linear down to 20 µg/L in plasma and down to 5 µg/L in saline as a surrogate for microdialysate. The lowest concentration on the calibration curve was taken as the lower limit of quantification (LLOQ), and measured concentrations below the LLOQ were imputed as "missing". Based on in-process quality controls (QCs), the coefficient of variation of the intra-/inter-assay precision of the determination of the total plasma concentration (C_{total}) or that in saline as a surrogate for microdialysate was < 6%. The accuracy was 100.1% in plasma and 98.9% in saline, respectively. Free concentrations (C_{free}) were determined after ultrafiltration

as previously described [13]. The unbound fraction ($f_u = C_{free}/C_{total}$) of tigecycline in QC samples (pooled plasma of healthy subjects spiked with 1 or 0.2 mg/L tigecycline) was 43.2 ± 7.9% at 1 mg/L and 61.1 ± 7.6% at 0.2 mg/L. The concentrations of total/free tigecycline in reanalysed patient plasma samples amounted to 101.9 ± 6.4% ($n = 61$, range 0.061–1.33 mg/L)/106.9 ± 4.7% ($n = 12$, range 0.067–1.22 mg/L) of the first analysis. The accuracy of the determination of free drug cannot be specified, as the extent of protein binding in a particular sample is unknown.

In the observed concentration range, there was a linear relationship between f_u and the logarithm of total plasma concentration (C_{total}), i.e. $f_u = -A_i \times \ln C_{total} + B_i$, with A_i being the slope and B_i being the y intercept of the individual linear regression line (supplementary Fig. S1). A_i and B_i were estimated individually for each patient based on measured free concentrations after 0.5, 2 and 8 h (high, medium and low concentrations). For the description of the entire free concentration–time curve, free concentrations for all sampling times were calculated according to $C_{free} = (-A_i \times \ln C_{tot} + B_i) \times C_{tot}$. The good correlation ($R = 0.9958$) of measured and calculated free concentrations demonstrates the appropriateness of this approach (supplementary Fig. S2).

Non-compartmental pharmacokinetic analysis was carried out using Phoenix WinNonlin 8.3 (Certara, Princeton, NJ, USA). The linear-up log-down trapezoidal rule was used for the calculation of the AUC from 0 to 8 h (AUC_{8h}). Clearance and volume of distribution were not determined, as the measuring interval of 8 h did not include the terminal elimination phase of tigecycline. The extrapolated AUC from 8 h to infinity, as estimated using the plasma half-life between 2 and 8 h, exceeded by far the limit of 20% of the total AUC (30.1 ± 7.1%/36.6 ± 7.6% for total/free plasma concentrations) [14]. The pharmacokinetic parameters of tigecycline in ISF were calculated separately for both probes and then averaged. Prism 8 (GraphPad Software, La Jolla, CA, USA) was used for calculating statistics. Results are given as mean ± SD if not stated otherwise. Comparisons between groups were made using the Welch t test or the Mann–Whitney U test, as appropriate. A p value < 0.05 was considered statistically significant.

3 Results

A total of 30 patients were included in the study. Fifteen obese patients (one class II, BMI 35.3 kg/m^2, and 14 class III, BMI 40.7–61.9 kg/m^2) undergoing bariatric surgery and 14 non-obese patients (BMI 21.1–27.5 kg/m^2) undergoing elective intra-abdominal surgery (mainly tumour resection) were evaluated. Both groups were comparable with respect to sex, age and kidney function. The differences in weight and BMI were large by definition (Table 1). One patient was excluded from the analysis, as the ISF concentrations could not be calculated due to missing retroperfusate solution, which is necessary for the calculation of the recovery [11]. Recovery was 37.1 ± 15.0% in the obese patients ($n = 15$) versus 38.4 ± 9.6% in the non-obese patients ($n = 14$). Both probes were evaluable in 28 patients. The recovery (mean, SD) of tigecycline in the right arm was 36.1 ± 13.4% and that in the left arm was 39.5 ± 14.9% ($p = 0.38$). The intra-individual variability of the recovery between the right and left arm was 36.1% in obese patients ($n = 14$) and 30.3% in non-obese patients ($n = 14$, $p = 0.61$). Nine patients in the obese group and five patients in the non-obese group erroneously received a 50 mg dose (one vial of tigecycline 50 mg) instead of the scheduled 100 mg dose (two vials of tigecycline 50 mg). To prevent the loss of statistical power, the concentrations were normalized to a 100-mg dose for the pharmacokinetic analysis. Due to the dose proportionality of total tigecycline concentrations in plasma, the measured total plasma concentrations were doubled in these patients [4]. Because of the atypical plasma protein binding behaviour of tigecycline, normalization of the free plasma concentrations from a 50-mg to a 100-mg dose resulted in an increase of the free concentrations by factors (median, range) of < 2 (obese 1.95, 1.86–1.97; non-obese 1.89, 1.82–1.97). As the ISF concentrations are in equilibrium with the free plasma concentrations, the same factors (specific for each patient and time point) were applied to ISF concentrations. The pharmacokinetic analysis was also performed using unnormalized concentrations stratified by dose as a sensitivity

Table 1 Patient characteristics (median, range)

Characteristic	Obese	Non-obese
n, sex	15 (5m, 10f)	14 (5m, 9f)
Age (years)	46 (24–61)	44 (25–62)
Height (cm)	171 (160–178)	170 (154–187)
Weight (kg)	149 (108–196)	70 (54–89)
BMI (kg/m^2)	1 class II (35.3) 14 class III 52.4 (40.7–61.9)	23.8 (21.1–27.5)
Albumin (g/L)	45.3 (41.7–50.3)	45.5 (36.4–48.7)
Total bilirubin (mg/dL)	0.45 (0.24–1.1)	0.34 (0.15–0.94)
SCrea (mg/dL)	0.86 (0.60–1.2)	0.74 (0.55–1.1)
eGFR[a]	92.4 (63.5–140)	102 (64.8–160)
Length of surgery[b] (h)	2.8 (1.2–5.3)	3.7 (1.3–8.6)
Vasopressors[c] (*n*, %)	7 (47%)	4 (29%)

BMI body mass index, *SCrea* serum creatinine, *eGFR* estimated glomerular filtration rate

[a]CKD-EPI formula [22]

[b]Time between skin incision and wound closure

[c]Noradrenaline or cafedrine/theodrenaline

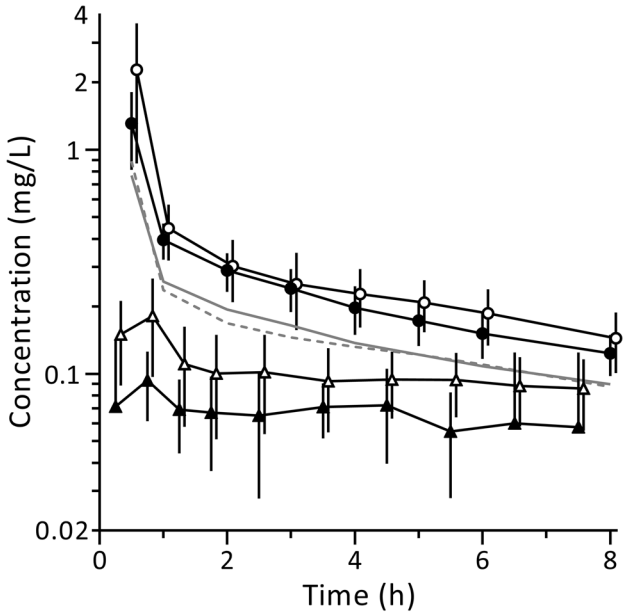

Fig. 1 Concentrations (mean, SD) of tigecycline in plasma (circles) or interstitial fluid (triangles) of obese (closed symbols) and non-obese (open symbols) surgical patients following a short intravenous infusion of 50 or 100 mg tigecycline (normalized to a dose of 100 mg). Grey lines mean free plasma concentrations (solid/dashed obese/non-obese, respectively)

analysis. The respective concentration–time curves as well as the results of this sensitivity analysis are included in the supplementary material (Fig. S3 and Table S1).

As shown in Fig. 1, the mean total plasma concentrations were higher in the non-obese patients and the difference was significant regarding the peak concentrations ($p = 0.028$). A fast decline within 30 min was followed by a slow decrease in concentrations. At the end of the measuring period after 8 h, the concentrations amounted to 10–15% of the peak concentrations. $AUC_{8h,plasma}$ was significantly lower in obese compared with non-obese patients ($p = 0.015$; Table 2). These differences were not observed in the free plasma concentrations due to a higher mean unbound fraction (mean ± SD) in obese (67.5 ± 10.7%) versus non-obese patients (54.2 ± 17.8%, cf. supplementary Fig. S1). The concentrations in subcutaneous ISF were lower than the corresponding free plasma concentrations, and the ISF concentrations in obese patients were lower than those in non-obese patients (Fig. 1). The percentage mean difference [95% confidence interval] in this primary endpoint ($AUC_{8h,ISF}$) was − 35% [− 56 to − 13] ($p = 0.0027$). Of note, sensitivity analysis using unnormalized concentrations stratified by dose gave similar results, with a loss of statistical significance in the 50-mg dose subgroup due to the reduced sample size: 50-mg subgroup − 34% [− 77 to + 9], 100-mg subgroup − 36% [− 63 to − 10]. The relative tissue drug exposure, expressed as $AUC_{8h,ISF}/fAUC_{8h,plasma}$, was 0.38 ± 0.19 in obese patients as opposed to 0.63 ± 0.24 in non-obese patients ($p = 0.0049$).

4 Discussion

The aim of the study was to describe the distribution of tigecycline in subcutaneous tissue of obese patients using microdialysis. The strength of this study is the implementation of a control group of non-obese patients, thus avoiding errors

Table 2 Pharmacokinetic parameters (mean ± SD) of tigecycline in plasma and subcutaneous interstitial fluid (ISF) of patients following a short infusion of 50 or 100 mg tigecycline, normalized to a dose of 100 mg

Parameter	$Plasma_{total}$			$Plasma_{free}$			Subcutaneous interstitial fluid		
	Obese	Non-obese	Δ% [95% CI]	Obese	Non-obese	Δ% [95% CI]	Obese	Non-obese	Δ% [95% CI]
AUC_{8h} (h·mg/L)	2.15 ± 0.42	2.74 ± 0.73	**− 22% [− 38 to − 5]**	1.42 ± 0.28	1.40 ± 0.59	+ 2% [− 23 to + 27]	0.51 ± 0.22	0.79 ± 0.23	**− 35% [− 56 to − 13]**
C_{max} (mg/L)	1.31 ± 0.50	2.27 ± 1.40	**− 42% [− 77 to − 7]**	0.768 ± 0.305	0.888 ± 0.593	− 13% [− 54 to + 27]	0.135 ± 0.100	0.204 ± 0.069	**− 34% [− 66 to − 2]**
T_{max} (h)[a]	0.5	0.5	± 0%	0.5	0.5	± 0%	0.75 (0.25–7.5)	0.75 (0.25–7.5)	+ 40% [− 11 to + 140]
C_{8h} (mg/L)	0.12 ± 0.03	0.14 ± 0.04	− 16% [− 34 to + 1]	0.087 ± 0.019	0.087 ± 0.032	± 0% [− 23 to + 23]	0.043 ± 0.022	0.071 ± 0.023	**− 39% [− 62 to − 15]**
$AUC_{8h,ISF}/fAUC_{8h,plasma}$							0.375 ± 0.193	0.628 ± 0.243	**− 40% [− 67 to − 14]**

Δ% mean percentage difference, *CI* confidence interval, AUC_{8h} area under the concentration–time curve from 0 to 8 h, C_{max} peak concentration, T_{max} time to C_{max}, C_{8h} concentration at 8 h, $AUC_{8h,ISF}/fAUC_{8h,plasma}$ ratio of AUC_{8h} in ISF and AUC_{8h} of the free plasma concentration

[a]Median (range). Bold font indicates a statistically significant difference between the obese and non-obese group

which could result from comparison with historical data. The results of this study revealed that total plasma concentrations were significantly lower in obese patients compared to non-obese patients. In contrast, the free plasma concentrations were similar in both groups, as the mean unbound fraction was higher in obese patients. As there are no published data supporting reduced plasma protein in obesity, the question arises as to whether protein binding of tigecycline in the non-obese control group was increased [2]. Previously, it has been hypothesized that tigecycline could bind to alpha-1-acid glycoprotein (AGP), as it differs from the tetracycline minocycline by an added *tert*-butyl-glycylamido side chain with basic character [13]. With this in mind, the lower mean unbound fraction of tigecycline and the higher variability in the control group (coefficient of variance 32.8 vs 15.8% in the obese group) could be interpreted as a result of higher and more variable AGP concentrations in the more heterogeneous control group. Although AGP typically binds basic drugs, the interaction of tigecycline with AGP has not yet been investigated [15].

The concentrations of tigecycline in ISF were lower than the free concentrations in plasma and were lower in obese patients compared to non-obese patients. Impaired subcutaneous tissue distribution in obese patients has also been observed with other antibiotics, and has been explained by a reduced capillary permeability surface area and reduced blood flow in adipose tissue [16–20]. ISF concentrations of tigecycline equal to the free plasma concentrations have been observed in patients with diabetes after multiple dosing, i.e. under steady-state conditions [7]. However, concentrations of tigecycline exceeding the plasma concentrations have been measured in biopsies of gall bladder, colon and lung tissue after single-dose administration, but these homogenate concentrations are obviously more representative of the intracellular space and not the interstitial space, which is the main site of bacterial infections [6, 21].

Unfortunately, the study design (perioperative setting, single dosing and a sampling interval of 8 h, covering < 80% of the total AUC) did not allow for precise determination of the key pharmacokinetic parameter for multiple dosing, namely the clearance; nor for the evaluation of pharmacokinetic/pharmacodynamic indices for the estimation of therapeutic efficacy. Furthermore, in a previous study, we observed losses of tigecycline in microdialysate due to adsorption onto the collection vials (polystyrene). This could be prevented by adding methanol (containing the internal standard minocycline) to the collection vials prior to HPLC analysis [13]. However, no experiments were performed to assess possible losses due to adsorption onto surfaces of the microdialysis probe, i.e. the membrane (polyarylethersulfone) or the outlet tube (polyurethane). Therefore, we cannot rule out false low initial concentrations of tigecycline in microdialysate (in both groups) before the plastic walls are saturated.

5 Conclusion

In view of the decreased concentrations of ticecycline in the ISF of subcutaneous adipose tissue in heavily obese patients following single-dose administration, doubling the loading dose in these patients seems to be appropriate. Due to the short time schedule, the clearance, a decisive parameter for multiple dosing, could not be determined. Further studies addressing the impact of obesity on the pharmacokinetics of tigecycline after multiple dosing are warranted.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13318-022-00789-2.

Declarations

Funding Open Access funding enabled and organized by Projekt DEAL. This trial was funded by the Federal Ministry of Education and Research, Germany (Integrated Research and Treatment Centre IFB "Adiposity Diseases", FKZ: 01E01001), and by departmental funding.

Conflict of interest CK reports research grants for PharMetrX, DDMoRe, FAIR. HW received grants from Pfizer (Investigator Initiated Trial Program, Berlin, Germany) and InfectoPharm (Heppenheim, Germany), both for the clinical microdialysis trial. HW reports lecture fees from InfectoPharm (Heppenheim, Germany), MSD (Konstanz, Germany), Getinge (Rastatt, Germany) and Medtronic (Meerbusch, Germany) and consultant honoraria from Dräger Medical (Lübeck, Germany) and Liberate Medical (Crestwood, KY, USA). PS reports lecture fees from InfectoPharm (Heppenheim, Germany). The other authors have no conflicts of interest to declare.

Author contributions PS, HW, DP, FK and MZ contributed to the study conception and design. PS and DP collected the data. CD, AK and FK performed bioanalysis. CD and FK performed pharmacokinetic and statistical analysis. CD and FK drafted the manuscript; DP, AK, CK, MZ, HW and PS revised and edited the manuscript.

Ethics approval Approval for the trial was obtained from the Leipzig University ethics committee (121/13-ff) and the Federal Institute for Drugs and Medical Devices of Germany (BfArM).

Informed consent Prior written informed consent was obtained from all study participants.

Consent for publication Not appicable.

Code availability Not applicable.

Data availibility Data are available on reasonable request.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the

original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc/4.0/.

References

1. Alobaid AS, Hites M, Lipman J, Taccone FS, Roberts JA. Effect of obesity on the pharmacokinetics of antimicrobials in critically ill patients: a structured review. Int J Antimicrob Agents. 2016;47:259–68.
2. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. Clin Pharmacokinet. 2010;49:71–87.
3. Pai MP. Antimicrobial dosing in specific populations and novel clinical methodologies: obesity. Clin Pharmacol Ther. 2021;109:942–51.
4. Barbour A, Schmidt S, Ma B, Schiefelbein L, Rand KH, Burkhardt O, et al. Clinical pharmacokinetics and pharmacodynamics of tigecycline. Clin Pharmacokinet. 2009;48:575–84.
5. Wyeth Pharmaceuticals LLC. TYGACIL® (tigecycline) for injection, for intravenous use, Prescribing information [Internet]. 2021. Available from: https://labeling.pfizer.com/ShowLabeling.aspx?id=491.
6. Rodvold KA, Gotfried MH, Cwik M, Korth-Bradley JM, Dukart G, Ellis-Grosse EJ. Serum, tissue and body fluid concentrations of tigecycline after a single 100 mg dose. J Antimicrob Chemother. 2006;58:1221–9.
7. Bulik CC, Wiskirchen DE, Shepard A, Sutherland CA, Kuti JL, Nicolau DP. Tissue penetration and pharmacokinetics of tigecycline in diabetic patients with chronic wound infections described by using in vivo microdialysis. Antimicrob Agents Chemother. 2010;54:5209–13.
8. Grupper M, Nicolau DP. Obesity and skin and soft tissue infections: how to optimize antimicrobial usage for prevention and treatment? Curr Opin Infect Dis. 2017;30:180–91.
9. Pai MP. Serum and urine pharmacokinetics of tigecycline in obese class III and normal weight adults. J Antimicrob Chemother. 2014;69:190–9.
10. Ibrahim MM, Abuelmatty AM, Mohamed GH, Nasr MA, Hussein AK, Ebaed MED, et al. Best tigecycline dosing for treatment of infections caused by multidrug-resistant pathogens in critically ill patients with different body weights. Drug Design Dev Therapy. 2018;12:4171–9.
11. Simon P, Petroff D, Dorn C, Ehmann L, Kloft C, Prettin C, et al. Measurement of soft tissue drug concentrations in morbidly obese and non-obese patients—a prospective, parallel group, open-labeled, controlled, phase IV, single center clinical trial. Contemp Clin Trials Commun. 2019;15:100375.
12. Bouw MR, Hammarlund-Udenaes M. Methodological aspects of the use of a calibrator in in vivo microdialysis—further development of the retrodialysis method. Pharm Res. 1998;15:1673–9.
13. Dorn C, Kratzer A, Liebchen U, Schleibinger M, Murschhauser A, Schlossmann J, et al. Impact of experimental variables on the protein binding of tigecycline in human plasma as determined by ultrafiltration. J Pharm Sci. 2018;107(2):739–744.
14. Marzo A, Monti NC, Vuksic D. Experimental, extrapolated and truncated areas under the concentration–time curve in bioequivalence trials. Eur J Clin Pharmacol. 1999;55:627–31.
15. Celestin MN, Musteata FM. Impact of changes in free concentrations and drug-protein binding on drug dosing regimens in special populations and disease states. J Pharm Sci. 2021;110:3331–44.
16. Simon P, Petroff D, Busse D, Heyne J, Girrbach F, Dietrich A, et al. Meropenem plasma and interstitial soft tissue concentrations in obese and nonobese patients—a controlled clinical trial. Antibiotics. 2020;9:931.
17. Dorn C, Petroff D, Stoelzel M, Kees MG, Kratzer A, Dietrich A, et al. Perioperative administration of cefazolin and metronidazole in obese and non-obese patients: a pharmacokinetic study in plasma and interstitial fluid. J Antimicrob Chemother. 2021;76:2114–20.
18. Brill MJE, Houwink API, Schmidt S, Dongen EPAV, Hazebroek EJ, van Ramshorst B, et al. Reduced subcutaneous tissue distribution of cefazolin in morbidly obese versus non-obese patients determined using clinical microdialysis. J Antimicrob Chemother. 2014;69:715–23.
19. Simon P, Busse D, Petroff D, Dorn C, Ehmann L, Hochstädt S, et al. Linezolid concentrations in plasma and subcutaneous tissue are reduced in obese patients, resulting in a higher risk of underdosing in critically ill patients: a controlled clinical pharmacokinetic study. J Clin Med. 2020;9(4):1067.
20. Müller M, dela Peña A, Derendorf H. Issues in pharmacokinetics and pharmacodynamics of anti-infective agents: distribution in tissue. Antimicrob Agents Chemother. 2004;48:1441–53.
21. Liu P, Müller M, Derendorf H. Rational dosing of antibiotics: the use of plasma concentrations versus tissue concentrations. Int J Antimicrob Agents. 2002;19:285–90.
22. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–12.

Authors and Affiliations

Christoph Dorn[1] · David Petroff[2,3] · Alexander Kratzer[4] · Frieder Kees[5] · Charlotte Kloft[6] · Markus Zeitlinger[7] · Hermann Wrigge[3,8,9] · Philipp Simon[3,10]

[1] Institute of Pharmacy, University of Regensburg, 93040 Regensburg, Germany

[2] Clinical Trial Centre, University of Leipzig, Leipzig, Germany

[3] Integrated Research and Treatment Center (IFB) Adiposity Diseases, University of Leipzig, Leipzig, Germany

[4] Hospital Pharmacy, University Hospital Regensburg, Regensburg, Germany

[5] Department of Pharmacology, University of Regensburg, Regensburg, Germany

[6] Department of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Berlin, Germany

[7] Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria

[8] Department of Anaesthesiology, Intensive Care and Emergency Medicine, Pain Therapy, Bergmannstrost Hospital Halle, Halle, Germany

[9] Medical Faculty, Martin-Luther-University Halle/Wittenberg, Halle, Germany

[10] Anaesthesiology and Operative Intensive Care, Faculty of Medicine, University of Augsburg, Augsburg, Germany