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Perioperative administration of cefazolin and metronidazole in obese and non-obese patients: a pharmacokinetic study in plasma and interstitial fluid

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Objectives: To assess plasma and tissue pharmacokinetics of cefazolin and metronidazole in obese patients undergoing bariatric surgery and non-obese patients undergoing intra-abdominal surgery.

Patients and methods: Fifteen obese and 15 non-obese patients received an IV short infusion of 2 g cefazolin and 0.5 g metronidazole for perioperative prophylaxis. Plasma and microdialysate from subcutaneous tissue were sampled until 8 h after dosing. Drug concentrations were determined by HPLC-UV. Pharmacokinetic parameters were calculated non-compartmentally.

Results: In obese patients (BMI 39.5–69.3 kg/m^2) compared with non-obese patients (BMI 18.7–29.8 kg/m^2), mean C_{max} of total cefazolin in plasma was lower (115 versus 174 mg/L) and V_{ss} was higher (19.4 versus 14.2 L). The mean differences in $t_{1/2}$ (2.7 versus 2.4 h), CL (5.14 versus 4.63 L/h) and AUC_{∞} (402 versus 450 mg·h/L) were not significant. The influence of obesity on the pharmacokinetics of metronidazole was similar (C_{max} 8.99 versus 14.7 mg/L, V_{ss} 73.9 versus 51.8 L, $t_{1/2}$ 11.9 versus 9.1 h, CL 4.62 versus 4.13 L/h, AUC_{∞} 116 versus 127 mg·h/L). Regarding interstitial fluid (ISF), mean concentrations of cefazolin remained >4 mg/L until 6 h in both groups, and those of metronidazole up to 8 h in the non-obese group. In obese patients, the mean ISF concentrations of metronidazole were between 3 and 3.5 mg/L throughout the measuring interval.

Conclusions: During the time of surgery, cefazolin concentrations in plasma and ISF of subcutaneous tissue were lower in obese patients, but not clinically relevant. Regarding metronidazole, the respective differences were higher, and may influence dosing of metronidazole for perioperative prophylaxis in obese patients.

Introduction

Surgical site infections (SSIs) are among the most frequent types of healthcare-associated infections.[1] SSIs are associated with increased healthcare costs, risk of hospital re-admission and even mortality in the 30 day period following surgery.[1] The results of a large, multicentre cohort study indicated that being overweight or obese significantly increased the risk of SSI in a number of surgical categories.[2] Insufficient serum and tissue concentrations of antibiotics used for surgical prophylaxis are one of the explanations given for the increased risk in obese individuals.[1] A fixed dose of 2 g cefazolin is frequently used for perioperative prophylaxis covering typical Gram-positive and some Gram-negative pathogens. Metronidazole (0.5 g) is used as an adjunct for intra-abdominal surgery if enteric anaerobic contamination is possible.[3] Increased dosage regimens of cefazolin for surgical prophylaxis are recommended by French and American guidelines in patients with a BMI of ≥35 kg/m^2 or with a total body weight (TBW) of ≥120 kg,

but there is still an open discussion on the appropriate dosing in obesity.[1] Different conclusions were drawn depending on whether the approach was based on pharmacokinetic (PK) considerations, on target concentrations or on the rate of postoperative infections.[4–11] Comparable studies on metronidazole are lacking.

The aim of the present study was to provide data on the PK of 2 g cefazolin and 0.5 g metronidazole administered for perioperative prophylaxis in plasma and subcutaneous tissue of obese patients undergoing bariatric surgery, compared with a non-obese control group undergoing elective abdominal surgery. Microdialysis was used, which allows measurement of the concentration in interstitial fluid (ISF), the main site of bacterial infections.[12]

Patients and methods

Study design and patients

This prospective, monocentric, controlled clinical trial was conducted as part of a larger PK study (EudraCT No. 2012-004383-22) at the Department of Anaesthesiology and Intensive Care Medicine, University of Leipzig Medical Center, Germany. The study protocol was approved by the competent ethics committee (No. 121/13-ff) and the Federal Institute for Drugs and Medical Devices of Germany. Class II (BMI 35–39.9 kg/m^2) or class III (BMI $\geq$ 40 kg/m^2) obese patients, scheduled for elective bariatric surgery, were eligible for the study. Non-obese patients (BMI < 30 kg/m^2) undergoing elective laparoscopic or open abdominal surgery were matched for sex and age, with a tolerance of 5 years for the latter. Major exclusion criteria were: pregnancy or breastfeeding; known allergy to the study drugs; and severe liver or kidney disease. Prior written informed consent was obtained from all study participants. Further details on the study protocol have been described previously.[13]

Study procedure

Microdialysis probes (CMA 63 microdialysis probe, cut-off 20 000 Da, membrane length 30 mm, CMA, Kista, Sweden) were inserted subcutaneously into both upper arms (one probe per arm). The probes were constantly perfused with saline at 2.0 μL/min. Two grams of cefazolin (Cephazolin, Fresenius Kabi, Bad Homburg, Germany) and 0.5 g metronidazole (Metronidazol, Fresenius Kabi, Bad Homburg, Germany) were administered concomitantly as short infusion (median 25 min, range 21–30 min) starting 30 min (median, range 3–71 min) prior to incision as part of perioperative prophylaxis. In the case of prolonged surgical interventions (>4 h), 1.5 g cefuroxime was given according to the clinical standard. Anaesthesia was left to the discretion of the anaesthetist. Blood samples were collected with Lithium Heparin S-Monovettes (Sarstedt, Nümbrecht, Germany) predose and after 0.5 (end of infusion), 1, 2, 3, 4, 5, 6 and 8 h. Microdialysate was collected from −1 to 0 h (baseline), 0–0.5, 0.5–1, 1.0–1.5, 1.5–2.0, 2–3, 3–4, 4–5, 5–6, 6–7 and 7–8 h. After the sampling period, the probes were calibrated using the 'retrodialysis-by-drug' method.[14] After perfusion of the probes (5 min × 15 μL/min) with 10 mg/L cefazolin in saline, retrodialysis was started at 2.0 μL/min, and dialysate was collected for 30 min. Thereafter the procedure was repeated with 5 mg/L metronidazole. The *in vivo* relative recovery by loss was corrected for residual tissue concentrations as suggested previously: recovery (%) = $[(C_{in} + C_{ext}) - C_{out}]/C_{in} \times 100$, where C_{in} and C_{out} are the perfusate and dialysate concentrations of the drugs during retrodialysis and C_{ext} is the extrapolated dialysate concentration at the midpoint of the retrodialysis period.[15] The concentrations of C_{ext} compared with C_{in} were relatively high in some obese patients: cefazolin (median, min–max) 2.8% (0.53%–29%); metronidazole 16% (7.3%–36%). As residual concentrations affect the precision of the calculated recovery and the error increases with increasing C_{ext}/C_{in} ratio, the protocol was changed to a C_{in} of 50 mg/L for both drugs for the subsequent study in non-obese patients.[13] The C_{ext} was then negligible for cefazolin [0.95% (0.07%–2.7%) of C_{in}] and 3.4% (0.75%–8.7%) for metronidazole, respectively, i.e. slightly lower than found previously.[15] The ISF concentrations (C_{ISF}) were calculated according to $C_{ISF} = C_{dialysate} \times 100$/recovery (%). The free plasma concentrations were measured in the 0.5, 1, 4 and 8 h samples to calculate the unbound fraction (f_u). Cefazolin showed a linear relationship between f_u and total concentration within the observed concentration range. The individually calculated linear regressions were used to calculate the concentration–time course of free cefazolin. There was a good agreement between calculated and measured free concentrations (bias 0.16%, 95% CI −12.1% to 12.4%). The f_u of metronidazole was independent of the concentration and amounted to 96.4% ± 4.4%, as calculated in 16 patients. The mean value was used to calculate the concentration–time course of free metronidazole in all patients. $AUC_{ISF}/fAUC_{plasma}$ was calculated using the respective AUCs extrapolated to infinity (AUC_∞).

Drug assays

The concentrations of cefazolin and metronidazole were determined by HPLC-UV as previously described.[16] Based on in-process quality controls (QCs), imprecision and inaccuracy of the determination in microdialysate and of total drug in plasma were within 4% for both substances. Free concentrations were determined after ultrafiltration as previously described.[16] The accuracy of the determination of free drug cannot be specified, as the extent of protein binding in a particular sample is not known. The precision was assessed by analysing spiked pooled plasma of healthy subjects. The f_u of cefazolin in these QCs was 19.7% ± 0.9% at 100 mg/L and 14.9% ± 0.8% at 20 mg/L. The f_u of metronidazole was 96.6% ± 2.8% at 10 mg/L and 98.1% ± 2.4% at 2.0 mg/L.

Data analysis

Non-compartmental pharmacokinetic analysis (NCA) was carried out using Phoenix WinNonlin 8 (Certara, Princeton, NJ, USA). The elimination rate constant λ_z was determined by log-linear regression in the elimination phase and included typically the time interval from 4 to 8 h (plasma) or the 4–5 to 7–8 h fraction (ISF). The linear-up log-down trapezoidal rule was used for calculation of AUC_8. Extrapolation to infinity to get AUC_∞ was based on the predicted concentrations at 8 h. Prism 7 for Mac OS X (GraphPad Software, La Jolla, CA, USA) was used for calculating statistics. Results are given as mean ± SD if not stated otherwise. Comparison between groups was made using Student's unpaired *t*-test. Welch's correction was performed if required. A *P* value of <0.05 was considered statistically significant.

Results

Fifteen obese patients scheduled for bariatric surgery and 15 non-obese patients undergoing elective abdominal surgery (tumour resections of liver, pancreas, colon or cervix, $n = 7$; cysts of liver or ovaries, $n = 3$; uterus myomatosus, cholecystolithiasis, hernia, achalasia and hiatal hernia, $n = 1$ each) were enrolled in the study. No patients showed signs of acute infection or critical illness at the time of the surgery or during the first seven postoperative days. No drug-related adverse events were observed. Patient characteristics are summarized in Table 1, where one patient from the obese group is listed separately to provide additional information on a patient with unusual cefazolin PK. Both groups were comparable with respect to sex and age by design, and to kidney function as characterized by the estimated glomerular filtration rate (eGFR). The differences in weight and BMI were large by definition. The plasma data of all patients were evaluable. Regarding ISF, data from 4 out of 60 (cefazolin) and 8 out of 60 (metronidazole)

Table 1. Patient characteristics (median, min–max)

Characteristic	Obese		Non-obese
	Outlier	Rest	
Sex (male/female)	1 (male)	4/10	5/10
Age (years)	45	40.5 (25–65)	45 (21–65)
Height (cm)	168	173 (156–185)	168 (160–192)
Weight (kg)	163	155 (123–200)	78 (50–96)
BMI (kg/m^2)	57.8	51.7 (39.5–69.3)[a]	26.0 (18.7–29.8)
Albumin (g/L)	38.2	43.7 (39.5–48.4)	44.7 (42.0–50.8)
Serum creatinine[b] (mg/dL)	1.06	0.77 (0.52–1.32)	0.79 (0.61–1.14)
eGFR[c] (mL/min)	84.0[d]	95.5 (57.6–145.0)	92.7 (70.8–121.5)
Length of surgery[e] (h)	2.7	2.7 (1.4–3.9)	2.7 (0.83–8.0)
Vasopressors[f] (*n*, %)	1	5 (36)	7 (47)

One obese patient exhibiting outlying PK parameters (see Table 2) is listed separately.
[a]One patient with class II obesity (35.5 kg/m^2), 14 patients with class III obesity (46.1–69.3 kg/m^2).
[b]Nearest measurement before surgery.
[c]CKD-EPI equation.[41]
[d]112 mL/min the day after surgery.
[e]Time between skin incision and wound closure.
[f]Noradrenaline or cafedrine/theodrenaline.

probes were not evaluated (malfunction of probe, missing calibrator solution, implausible concentration in the calibrator solution). One further probe was excluded as an outlier based on the Tukey's test (cefazolin: $AUC_{ISF}/fAUC_{plasma}$ = 1.60 with an upper Tukey fence value of 1.55; Figure S1, available as Supplementary data at *JAC* Online). Microdialysis data of 29/27 (cefazolin/metronidazole) patients were evaluable; both probes were evaluable in 27/25 patients. The recovery between the right and left arm was comparable (cefazolin: 35.4%± 17.9% versus 37.4% ± 17.1%; metronidazole 53.1% ± 17.5% versus 50.5% ± 17.9%). The recovery in the obese group was significantly lower (cefazolin: 30.4% ± 11.8% versus 42.2% ± 16.8%, 95% CI for the mean difference −23.3 to −0.4; metronidazole: 41.8% ± 9.0% versus 62.7% ± 15.8%, 95% CI for the mean difference −31.3 to −10.6).

The concentration–time course of cefazolin in plasma and subcutaneous tissue is displayed in Figure 1 and Figure S2. One patient is depicted separately because of an exceptionally long plasma $t_{1/2}$ of 8.3 h despite apparently normal renal function (Table 1). The peak concentrations were distinctly lower in the obese group than in the non-obese group, but decreased more slowly with a flat interval between 3 and 4 h. This biphasic concentration–time course was more pronounced in ISF and particularly evident in the separately depicted patient, where a second peak was observed after 4.5 h. The mean free plasma concentrations as well as the ISF concentrations of cefazolin were, in both groups, >4 mg/L [epidemiological cut-off value (ECOFF) of *Escherichia coli*] until 6 h and >2 mg/L (ECOFF of *Staphylococcus aureus*) until 8 h.[17] The PK parameters of cefazolin are summarized in Table 2. C_{max} was lower and V_{ss} was higher in the obese group, whereas the differences in CL, AUC_∞ or relative drug exposure in ISF ($AUC_{ISF}/fAUC_{plasma}$) were not significant. The difference in $fAUC_\infty$ was just significant. The concentration–time course of metronidazole in plasma and ISF is displayed in Figure 2 and Figure S3; the PK parameters are listed in Table 3. As with cefazolin, C_{max} of metronidazole was lower and V_{ss} was higher in the obese group, whereas the differences in CL, AUC_∞ or $AUC_{ISF}/fAUC_{plasma}$ were not significant. The mean ISF concentrations of metronidazole in the non-obese group were >4 mg/L for up to 8 h (the EUCAST breakpoint for Gram-negative anaerobes was used alternatively, as no ECOFF values are available),[17] whereas those in the obese group were between 3 and 3.5 mg/L throughout the measuring interval.

Discussion

The aim of the study was to assess the plasma and tissue concentrations of cefazolin and metronidazole in obese surgical patients compared with a non-obese control group. Microdialysis was applied as the currently most appropriate sampling technique to investigate the tissue penetration, in particular into the interstitial space, the main site of bacterial infections.[12] As concentrations in the ISF are better correlated with the free than with the total plasma concentrations, the free plasma concentrations were measured too.[12]

The PK parameters of cefazolin in the control group were in good agreement with previous data in normal subjects; the $t_{1/2}$ was somewhat longer, in agreement with results in surgical patients.[18,19] As also previously described, protein binding was moderately dependent on the concentration, with an f_u of about 30% at peak concentrations and 20% after 8 h.[19,20] In the obese patients, the mean peak concentrations were significantly lower than in non-obese patients (plasma: 115 versus 174 mg/L; ISF: 13.3 versus 24.4 mg/L), but the concentrations decreased more slowly. The lower peak concentrations in plasma and ISF reflect the higher *V* in the obese patients; the lower decrease in ISF compared with plasma indicates impaired equilibration between tissue and plasma during the surgery. The following parallel decrease in ISF and plasma indicates the normalization of the kinetic processes after the end of surgery. These kinetic processes became

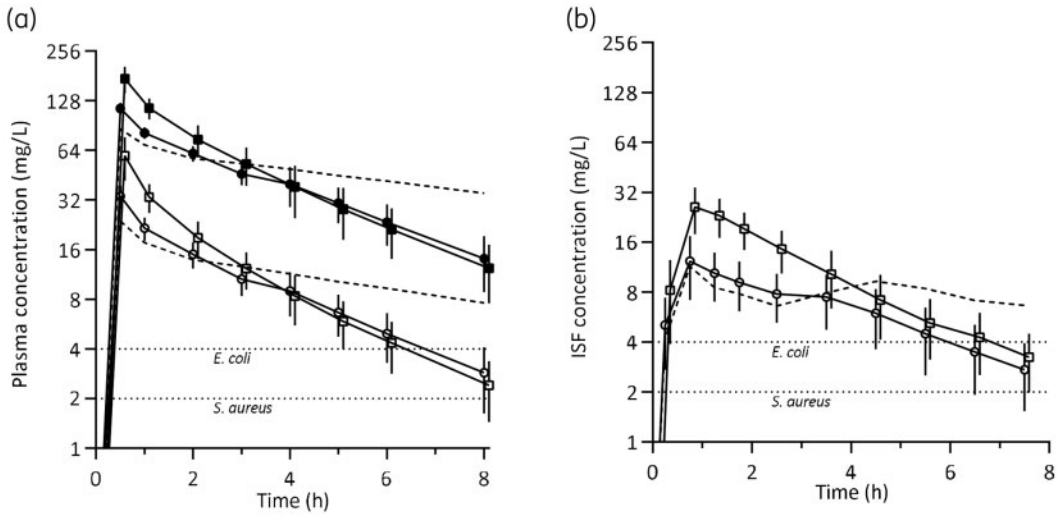

Figure 1. Concentration–time course (mean, SD) of cefazolin in plasma (a) and ISF of subcutaneous tissue (b) in obese (circles) and non-obese (squares) patients following a single IV short infusion of 2 g cefazolin. Closed/open = total/free concentrations, broken line = outlying patient in the obese group. Dotted lines: ECOFF for *S. aureus* or *E. coli*.[17] Individual concentration–time courses are shown in Figure S2.

Table 2. PK parameters (mean ± SD) of cefazolin in plasma and ISF of subcutaneous tissue of surgical patients after a single IV short infusion of 2 g cefazolin

Parameter		Plasma				ISF of subcutaneous tissue			
		Obese			95% CI for the mean difference	Obese			95% CI for the mean difference
		Outlier	Rest	Non-obese		Outlier	Rest	Non-obese	
n		1[a]	14	15		1[a]	14	14	
C_{max} (mg/L)	t	86.1	114.6 ± 9.3	174 ± 31	−77.4 to −40.9				
	f	22.8	33.3 ± 3.6	60.0 ± 16.2	−36.2 to −17.2	11.6	13.0 ± 4.4	24.4 ± 7.4	−16.3 to −6.5
f_u (%)		28.8	29.8 ± 2.8	34.7 ± 4.8	−7.9 to −1.7				
T_{max} (h)[b]		0.5 h (end of infusion)				1.25	0.75, 0.25–4.5	0.75, 0.75–1.75	
C_8 (mg/L)	t	35.2	14.1 ± 5.1	12.2 ± 4.6	−1.9 to 5.7				
	f	7.80	2.89 ± 1.11	2.37 ± 0.98	−0.41 to 1.24	6.20	2.27 ± 1.10	2.53 ± 1.04	−1.12 to 0.62
f_u (%)		22.3	20.0 ± 1.9	20.0 ± 4.4	−2.8 to 2.6				
$t_{1/2}$ (h)	t	8.34	2.70 ± 0.60	2.41 ± 0.38	−0.11 to 0.67				
	f	7.21	2.46 ± 0.50	2.21 ± 0.32	−0.08 to 0.58	6.28	2.57 ± 0.52	2.72 ± 0.53	−0.57 to 0.27
V_{ss} (L)	t	28.9	19.4 ± 1.2	14.2 ± 2.3	3.8–6.7				
CL_{total} (L/h)	t	2.44	5.14 ± 0.90	4.63 ± 0.94	−0.23 to 1.23				
AUC_{∞} (h·mg/L)	t	821	402 ± 75	450 ± 97	−117 to 20				
$fAUC_{\infty}$ (h·mg/L)	f	135	94.5 ± 16.9	117 ± 29	−41.3 to −3.99	121	58.3 ± 20.0	84.6 ± 21.9	−43.2 to −9.4
$AUC_{ISF}/fAUC_{plasma}$[c]						0.69	0.61 ± 0.17	0.75 ± 0.23	−0.30 to 0.018

t, total; f, free.
[a]Listed separately because of outlying PK parameters.
[b]Median, min–max.
[c]AUCs extrapolated to infinity have been used.

particularly visible in the patient with an exceptionally long $t_{1/2}$ of cefazolin and in the obese group regarding metronidazole in ISF, where a small increase of the concentrations was observed after the end of surgery. Similar concentration–time courses have also been observed with other antibiotics such as linezolid, cefazolin, cefuroxime or piperacillin.[21–25] This discontinuous concentration–time course has been explained by the reduced intraoperative regional blood flow and is presumably confined to the surgical situation.[26] The reason for the tripled plasma $t_{1/2}$ of cefazolin in one patient is unknown. The *V* in this patient was exceptionally high and the CL was low (Table 2). Both parameters result in a prolonged $t_{1/2}$ ($t_{1/2} = \ln 2 \times V/CL$). Cefazolin is cleared by the kidneys and a tripling of the $t_{1/2}$ of cefazolin is expected in patients with creatinine clearance <30 mL/min.[18] However, the estimated CL_{CR} in this patient

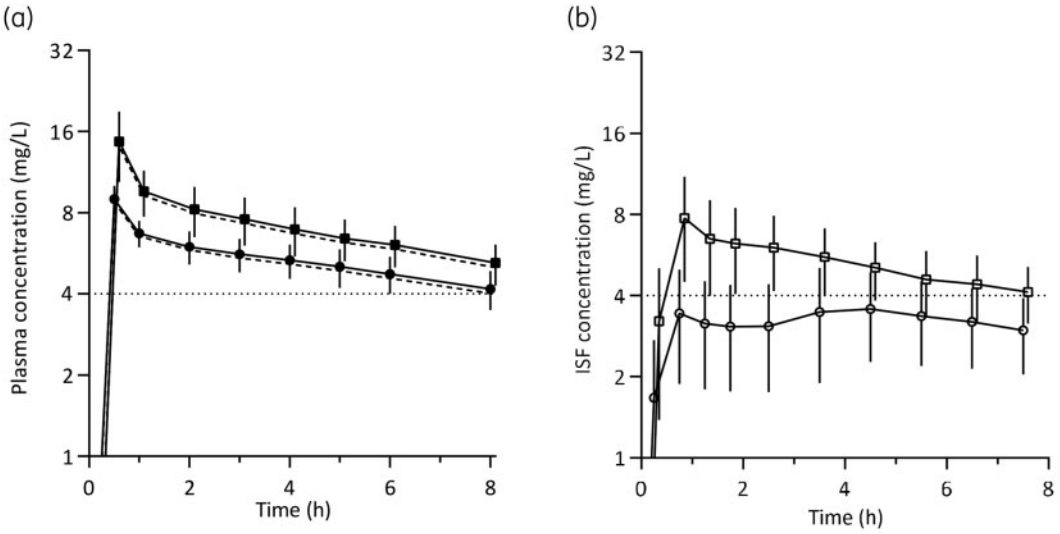

Figure 2. Concentration–time course (mean, SD) of metronidazole in plasma (a) and ISF of subcutaneous tissue (b) in obese (circles) and non-obese (squares) patients following a single IV short infusion of 0.5 g metronidazole. Broken line = calculated free plasma concentrations based on a mean f_u of 96.4%. Dotted lines = EUCAST MIC breakpoint for Gram-negative anaerobes.[17] Individual concentration–time courses are shown in Figure S3.

Table 3. PK parameters (mean ± SD) of metronidazole in plasma and ISF of subcutaneous tissue of surgical patients after a single IV short infusion of 0.5 g metronidazole

	Plasma			ISF of subcutaneous tissue		
Parameter	Obese	Non-obese	95% CI for the mean difference	Obese	Non-obese	95% CI for the mean difference
n	15	15		14	13	
C_{max} (mg/L)	8.99 ± 1.05	14.7 ± 4.1	−8.11 to −3.29	4.12 ± 1.58	8.83 ± 3.93	−7.29 to −2.12
T_{max} (h)[a]	0.5 h (end of infusion)		0	3.5, 0.75–6.5	0.75, 0.75–7.5	0
C_8 (mg/L)	4.18 ± 0.68	5.19 ± 0.90	−1.63 to −0.42	2.95 ± 0.90	3.91 ± 1.24	−1.89 to −0.10
$t_{1/2}$ (h)	11.9 ± 3.4	9.08 ± 1.85	0.68 to 4.97	11.0 ± 3.1	8.30 ± 4.73	−0.54 to 6.03
V_{ss} (L)	73.9 ± 10.3	51.8 ± 9.7	14.3 to 29.8			
CL_{total} (L/h)	4.62 ± 1.22	4.13 ± 0.87	−0.34 to 1.30			
AUC_{∞} (h·mg/L)	115.8 ± 29.0	126.9 ± 29.6	−33.8 to 11.5	72.2 ± 25.8	89.9 ± 27.3	−39.6 to 4.1
$AUC_{ISF}/fAUC_{Plasma}$[b,c]				0.67 ± 0.32	0.76 ± 0.24	−0.33 to 0.14

[a]Median, min–max.
[b]AUCs extrapolated to infinity have been used.
[c]Based on a mean f_u of 96.4%.

was 85 mL/min preoperatively and 112 mL/min the day after surgery. Inhibition of tubular secretion of cefazolin could be an explanation,[27] but no co-medication known to inhibit tubular secretion of β-lactams was documented.

The PK parameters of cefazolin in plasma of obese patients as assessed in the present study are in good agreement with results from two previous studies, where the relative drug exposure in ISF of subcutaneous tissue was similar ($AUC_{ISF}/fAUC_{plasma}$ = 0.70, range 0.68–0.83, n = 9) or about 1 ($AUC_{ISF}/fAUC_{plasma}$ = 1.05 ± 0.49, n = 4).[7,21] Passive diffusion is the mechanism for drug exchange between plasma and interstitial space. After IV short infusion, not all drug penetrates into the ISF because of the concurrent elimination, and the $AUC_{ISF}/fAUC_{plasma}$ ratio will be <1. It will be closer to 1 in organs that are well supplied with blood, such as the liver, compared with subcutaneous tissue, and should go towards 1 at steady-state. The actual ratio will be influenced by several factors, e.g. patient characteristics, severity of illness or surgical procedures. Very low ratios have been found in patients with septic shock receiving piperacillin.[28] Values >1 have also been reported, but are difficult to explain.[29] Values <1 predominate in a comprehensive review.[30]

For perioperative prophylaxis, the antibiotic concentration at the target site should exceed the MICs of probable organisms associated with the procedure from the moment of incision until

surgical-site closure.[31] PK/pharmacodynamic (PK/PD) indices such as $\%T_{>MIC}$, C_{max}/MIC or AUC/MIC have been developed for antibiotic therapy and are not applicable for antibiotic prophylaxis.[32] In this context, we compared the concentrations of cefazolin and metronidazole in obese and non-obese patients with MIC values for probable pathogens associated with SSIs following intra-abdominal surgery (Figures 1 and 2).[17]

The plasma and tissue concentrations of cefazolin were lower in the obese group during the surgery, but elimination was slower. The postoperative concentrations and the time above relevant MICs were similar. If higher intraoperative concentrations are desired, an increased preoperative dose in obese patients is reasonable, as recommended by newer guidelines.[31] A 'more frequent re-dosing of cefazolin' (after 2 h), as concluded from dosing simulations in obese women undergoing Caesarean delivery, may be of minor importance.[33] This conclusion is consistent with meta-analyses pointing out that timing of preoperative dosing is more important than timing of re-dosing.[34,35]

As for metronidazole, the PK parameters in the non-obese control group matched well with historical data, though the sampling time of 8 h was too short for the precise calculation of terminal $t_{1/2}$ or AUC_{∞}. The mean extrapolated $AUC_{8-\infty}$ was 54% of AUC_{∞} (data not shown) and hence significantly above the suggested upper limit of 20%.[36] Nevertheless, the PK parameters as determined in the present study (Table 3) are in good-to-fair agreement with historical data in healthy subjects (V_{ss} 0.64–0.74 L/kg, $t_{1/2}$ 7.3–7.9 h, CL 3.9–5.0 L/h and AUC_{∞} 101–151 h·mg/L).[37] The ISF concentrations as found in the control group (decrease from 8 to 4 mg/L after 8 h) are also consistent with previous results in five patients undergoing elective gynaecological surgery.[38] In the obese group, the mean concentrations varied between 3 and 3.5 mg/L throughout the measuring interval, i.e. they were constantly <4 mg/L, the EUCAST MIC breakpoint for Gram-negative anaerobes.[17] A dose of 0.5 g metronidazole is considered to be effective for perioperative prophylaxis in non-obese patients,[31,39] but according to the results of the present study, a higher dose of metronidazole in obese patients would be reasonable. Of note, current guidelines of the French Society of Anesthesia and Intensive Care Medicine (SFAR) recommend 1 g metronidazole for perioperative prophylaxis, irrespective of body weight.[40]

The strength of this microdialysis study is the high number of patients. However, there are limitations. The patient's characteristics were comparable except for obesity, but the type, the severity and the duration of the surgery were very variable in the control group. The concomitant medication was not standardized, including the use of vasopressors, which could have had an impact on regional blood flow and tissue penetration. Additionally, for better comparability the probes were inserted in a pre-defined position (upper arms) remote from the actual surgical sites, where the concentrations could differ.

Conclusions

During the time of surgery, cefazolin concentrations in plasma and ISF of subcutaneous tissue were lower in obese patients, but not clinically relevant. Regarding metronidazole, the respective differences were greater, and may influence dosing of metronidazole for perioperative prophylaxis in obese patients.

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Transparency declarations

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Supplementary data

Figures S1 to S3 are available as Supplementary data at *JAC* Online.

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