International Journal of Antimicrobial Agents 48 (2016) 633–640

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Evaluation of total body weight and body mass index cut-offs for increased cefazolin dose for surgical prophylaxis

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ARTICLE INFO

Article history:
Received 26 April 2016
Accepted 13 August 2016

Keywords:
Obesity
Non-obese patients
β-Lactam antibiotics
Pharmacokinetics
Pharmacodynamics

ABSTRACT

French and American guidelines recommend increased dosage regimens of cefazolin (CFZ) for surgical prophylaxis in patients with a body mass index (BMI) ≥ 35 kg/m^2 or with a total body weight (TBW) ≥ 120 kg. The objective of this study was to evaluate the accuracy of these cut-offs in identifying patients who require CFZ dose adjustment. A pharmacokinetic study was conducted in patients of varying TBW and BMI who received 2 g of CFZ intravenously for prophylaxis prior to digestive surgery. Adequacy of therapy, defined as a serum concentration of unbound CFZ (*f*CFZ) ≥ 4 mg/L, was evaluated 180 min (T_{180}) and 240 min (T_{240}) after the start of CFZ infusion. Possible factors associated with insufficient *f*CFZ levels were also assessed. A *P*-value of <0.05 was considered statistically significant. A total of 63 patients were included in the study, categorised according to BMI (<35 kg/m^2, 20 patients; and ≥35 kg/m^2, 43 patients) and TBW (<120 kg, 41 patients; and ≥120 kg, 22 patients). All patients had adequate drug levels at T_{180} but only 40/63 patients (63%) had adequate levels at T_{240}. At T_{240}, therapy was adequate in 15/20 patients (75%) and 25/43 patients (58%) with BMI <35 kg/m^2 and ≥35 kg/m^2, respectively ($P = 0.20$), and in 28/41 patients (68%) and 12/22 patients (55%) with TBW <120 kg and ≥120 kg, respectively ($P = 0.28$). No factor associated with insufficient *f*CFZ was identified. In conclusion, current BMI and TBW cut-offs are poor indicators of which patients could benefit from increased CFZ dosage regimens.

1. Introduction

A recent survey in the USA reported that surgical site infections (SSIs) are among the most frequent type (22%) of healthcare-associated infections [1]. Such infections are associated with increased healthcare costs, increased risk of hospital re-admission and increased mortality in the 30-day period following surgery [2]. Obesity, defined as a body mass index (BMI) ≥ 30 kg/m^2, is one of the risk factors for developing these post-operative infections [3–6].

Insufficient serum and tissue concentrations of antibiotics used for surgical prophylaxis are one of the explanations given for the increased risk of infection observed in obese individuals. Cefazolin (CFZ), a hydrophilic, strongly protein-bound (80%), first-generation cephalosporin eliminated primarily by the kidneys is most often the drug of choice for prophylaxis [7]. Despite an estimated 600 million obese adults worldwide [8] and a significant increase in the number of obese surgical patients over the past 20 years [9,10], the optimal prophylactic dose of CFZ for obese individuals has not yet been established.

Recent guidelines on antibiotic use for surgical prophylaxis provide some recommendations on CFZ dosage regimens for obese individuals. However, these recommendations are based on expert opinion and are supported by limited data showing that the pharmacokinetics of CFZ is altered in obese patients. Serum and/or tissue concentrations of CFZ are lower in obese compared with non-obese patients after administering the same antibiotic dose [11–14]. The French Infectious Diseases Society (SPILF) and the French Society of Anaesthesia and Resuscitation (SFAR) have, since 2010, recommended an increased dosage regimen of CFZ in heavier patients: 2 g for patients with a BMI < 35 kg/m^2 and 4 g for those with a

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http://dx.doi.org/10.1016/j.ijantimicag.2016.08.019

BMI ≥ 35 kg/m² [15]. Since 2013, the Infectious Diseases Society of America (IDSA) has recommended giving 2 g of CFZ to patients with a total body weight (TBW) of <120 kg and 3 g to those weighing ≥120 kg. The dose is to be repeated after 4 h if surgery is ongoing and the patient does not have renal insufficiency [7].

Since the publication of these guidelines, only two studies have evaluated the clinical relevance of these recommendations in non-pregnant adults. One retrospective clinical study performed in a cohort of 198 surgical patients concluded that there was little evidence for increasing CFZ dosage regimens in obese patients because SSI rates were similar in obese and non-obese patients. However, the study was underpowered to show any differences and the cohorts were not stratified by the recommended cut-offs, as the mean TBW and BMI values for the two groups were 90 kg vs. 110 kg and 27 kg/m² vs. 35 kg/m², respectively [16]. Another pharmacokinetic (PK) study on CFZ in eight morbidly obese and seven non-obese individuals confirmed significant PK changes in morbidly obese patients, attributed to changes in TBW; the authors recommended using 3 g of CFZ for prophylaxis in morbidly obese patients [17]. However, the optimal BMI or TBW cut-off at which the CFZ dosage regimen should be increased was not identified.

The objective of this study was therefore to evaluate whether the proposed BMI and/or TBW cut-offs could accurately identify which patients require CFZ dose adjustment for surgical prophylaxis.

2. Patients and methods

2.1. Study design and patient selection

This prospective study was performed at Erasme Hospital, the academic hospital of the Université Libre de Bruxelles in Brussels, Belgium. All consecutive, consenting patients undergoing gastric bypass surgery, partial hepatectomy, duodenopancreatectomy or colectomy between October 2011 and October 2013 were included. These surgical procedures were selected because only patients who would need central lines during surgery could be included in the study and, in our institution, central venous catheters are not inserted for uncomplicated routine surgical interventions. At 30–60 min prior to surgery, all patients receive a 2 g intravenous (i.v.) dose of CFZ over 30 min for surgical prophylaxis. Patients were excluded from the study if they were pregnant or lactating, were <18 years old, had a known allergy to β-lactams, had a serum creatinine level >1.3 mg/dL, had peripheral oedema and/or had pre-operative signs of hepatic dysfunction (total bilirubin levels > 2.5 mg/dL, altered coagulation and/or albuminaemia < 32 g/L). Patients were excluded from the analysis if blood loss was >1 L during the sampling period of the study because significant blood loss has been associated with antibiotic PK changes [7,18].

To ensure a similar distribution of patients of different sizes, patients were stratified into different groups of BMI as they were enrolled: <30 kg/m², 30–39 kg/m² and ≥40 kg/m². Patient enrolment for each group was stopped when a minimum of 10 patients and a maximum of 30 patients had been included, or when the 2-year study period came to an end. For data analysis, patients were then categorised into both a BMI group (<35 kg/m² or ≥35 kg/m²) and a TBW group (<120 kg or ≥120 kg).

2.2. Data collection

Demographic data and co-morbidities were recorded. Patients were weighed on the day prior to surgery and their height and abdominal circumference were measured. The BMI was calculated using the following equation: weight (kg)/height (m²) [19]. Blood loss and volume of fluid administered during the 180 min after the start of the CFZ infusion were recorded. The occurrence of a SSI (as defined by the IDSA) [7] in the 30 days following the surgical procedure was recorded.

2.3. Serum samples during the surgical procedure

A central venous line was placed in all patients after induction of anaesthesia for surgery. Two blood samples (3 mL) were collected from the central line into polypropylene Venosafe® VF-054SAS serum tubes (Terumo, Leuven, Belgium) immediately prior to the CFZ infusion (T_0). One serum sample was collected at each of the following time points after the start of the CFZ infusion: 30 min (T_{30}); 60 min (T_{60}); 120 min (T_{120}); and 180 min (T_{180}). A final serum sample was taken at the end of the surgical procedure, except in patients undergoing partial hepatectomy. In these patients, sampling was stopped at T_{180}, before portal triad clamping and resection of the liver, to limit any potential PK changes associated with this type of surgery [20].

After each serum sampling, the catheter was purged with 10 mL of physiological serum. Exact sampling times were recorded. Samples were kept on ice and were sent directly to the clinical chemistry laboratory where they were centrifuged at 3000 rpm at 4 °C for 10 min before the supernatant was removed and then frozen at –80 °C to be analysed at a later date.

2.4. Measurement of cefazolin serum concentrations

A modified liquid chromatography–ultraviolet spectrophotometry technique was used to measure CFZ levels [21]. Analyses were conducted using an ACQUITY UPLC® (ultra performance liquid chromatography) system (Waters, Zellik, Belgium). The UPLC separation was carried out at 50 °C. The mobile phase consisting of acetonitrile and phosphate buffer (0.3% phosphate buffer/acetonitrile 98:2 v/v) (pH 5.0) was delivered at a flow rate of 0.6 mL/min. Six-level aqueous calibrators with concentrations of CFZ ranging from 1 mg/L to 150 mg/L were employed for quantification of total CFZ (*t*CFZ) and unbound (free) CFZ (*f*CFZ) serum concentrations. For *t*CFZ, 50 μL of the internal standard solution (cefoperazone 200 mg/L) was added to 200 μL of thawed sample, precipitation of serum proteins was performed by adding 800 μL of methanol, and the mixture was then vortex-mixed. Following evaporation under nitrogen, the residue was reconstituted with 300 μL of phosphate buffer and was vortex-mixed for UPLC analysis. For *f*CFZ, 500 μL of sample was subjected to filtration using a Centrifree® device (Merck Millipore, Overijse, Belgium) by centrifugation (two times at 4000 rpm) for 10 min at 4 °C. The filtrate was mixed with 25 μL of the internal standard solution and was used as such for UPLC analysis. The coefficients of variation for CFZ were <6.7% for mean concentrations varying from 19.8 mg/L to 102 mg/L.

2.5. Measurement of renal function

Pre-operative serum creatinine levels were recorded. Serum and urinary creatinine were measured using a Hitachi Modular P analyser based on the Jaffé method [22] on a serum and urine sample (from a 24-h collect) taken on the day following the surgical intervention. Creatinine clearance (CL_{Cr}) was calculated using the following equation: $CL_{Cr,24h}$ (mL/min) = [urine creatinine (mg/dL) × volume (mL)]/[plasma creatinine concentration on the day of the urine collect (mg/dL) × 1440 min].

2.6. Free fatty acid and plasma protein determination

Serum albumin, α-1-acid glycoprotein, total proteins and free fatty acids were measured on the T_0 serum sample using a Hitachi Modular analyser (Roche Diagnostics, Vilvoorde, Belgium) according to the manufacturer's instructions.

2.7. Estimation of unbound cefazolin serum concentrations at T_{240}

Considering that most of the sampling was performed during the CFZ elimination phase, the following equation: $[\ln C_t = -k_e t + \ln C_0]$ was used to determine the terminal elimination rate constant (k_e) and to estimate the serum concentrations of the drug at C_0, where C_t is the measured serum concentration at the specified time and C_0 is the virtual serum concentration at the beginning of the elimination phase [23]. Estimated serum concentrations of *f*CFZ and *t*CFZ at T_{240} (when measured samples were not available) were determined based on extrapolation of the linear logarithmic *f*CFZ and *t*CFZ elimination equation until T_{240}. To validate the extrapolation method, estimated serum concentrations of *f*CFZ were determined for all measured *f*CFZ values during the elimination phase (corresponding to samples taken from T_{60} onwards) and were compared. Subgroups were also compared: serum samples taken at T_{240}; and all serum samples with a measured *f*CFZ concentration <12 mg/L, corresponding to the serum concentrations most likely to be found at T_{240}. Graphs of estimated *f*CFZ values as a function of measured values were also drawn.

2.8. Pharmacokinetic analyses

PK parameters were calculated using non-compartmental analysis. The area under the concentration–time curve (AUC) and the area under the first moment curve (AUMC) for *f*CFZ and *t*CFZ plasma profiles were calculated using the linear trapezoidal method and were extrapolated to infinity where $AUC_{0-\infty}$ was defined as $AUC_{0-last} + C_{last}/k_e$, and $AUMC_{0-\infty}$ was defined as $AUMC_{0-last} + (t \times C_{last}/k_e) + C_{last}/k_e^2$, and C_{last} corresponds to the last measured *f*CFZ or *t*CFZ serum concentration. The total body clearance (CL) and apparent volume of distribution (V_d) of *f*CFZ and *t*CFZ were then calculated using the following equations: $CL_{fCFZ \text{ or } tCFZ}$ = total dose of CFZ administered/$AUC_{0-\infty}$ and $V_{d,fCFZ \text{ or } tCFZ}$ = (AUMC × total dose of CFZ administered)/($AUC_{0-\infty}^2$). The mean residence time (MRT) was defined as $AUMC_{0-\infty}/AUC_{0-\infty}$ minus mean infusion time, which was defined as infusion time/2. The mean elimination rate constant (k) could then be calculated by k = 1/MRT. The terminal elimination half-life ($t_{1/2}$) for *f*CFZ and *t*CFZ were then calculated using $t_{1/2} = 0.693/k$ [24].

2.8.1. Adequacy of unbound cefazolin concentrations

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI) have defined clinical breakpoints for micro-organisms for different antimicrobial therapies by taking into account in vitro and in vivo pharmacokinetic/pharmacodynamic (PK/PD) data. β-Lactam antibiotics are time-dependent drugs [25], meaning that the PK/PD parameter that best describes their efficacy is the time that the concentration of unbound antibiotic remains above the minimum inhibitory concentration (MIC) of the bacteria ($fT_{>MIC}$) [26]. Based on expert opinion, to deliver appropriate antibiotic therapy for surgical prophylaxis, the dose and timing of antibiotic administration need to ensure that serum and tissue concentrations remain above the MIC of the most likely pathogens during the entire surgical procedure [7]. For digestive surgery, prophylactic antibiotics should be active against Enterobacteriaceae and *Staphylococcus* spp. For Enterobacteriaceae, the clinical breakpoints for CFZ are 1 mg/L according to the CLSI [27], whereas EUCAST no longer reports this value [28]. For methicillin-susceptible *Staphylococcus* spp., clinical breakpoints are 4 mg/L according to the CLSI and EUCAST [27,28]. For the current study, we therefore defined adequate serum concentrations as *f*CFZ ≥ 4 mg/L.

Table 1
Characteristics of patients ($n = 63$) according to body mass index (BMI) and total body weight (TWB).

Characteristic	BMI			TBW		
	<35 kg/m² ($n = 20$)	≥35 kg/m² ($n = 43$)	*P*-value	<120 kg ($n = 41$)	≥120 kg ($n = 22$)	*P*-value
Age (years)	48 ± 14	44 ± 10	0.11	47 ± 11	43 ± 10	0.14
Male sex	6 (30)	11 (26)	0.71	6 (15)	11 (50)	<0.01
Height (m)	1.70 ± 0.09	1.69 ± 0.10	0.72	1.66 ± 0.09	1.74 ± 0.09	<0.01
Abdominal circuference (cm)	103 ± 12	128 ± 13	<0.01	112 ± 14	136 ± 11	<0.01
BMI (kg/m²)	28 ± 5	43 ± 5	<0.01	34 ± 7	46 ± 5	<0.01
TBW (kg)	80 ± 15	122 ± 20	<0.01	92 ± 16	138 ± 11	<0.01
Co-morbidities						
Hypertension	2 (10)	9 (21)	0.48	5 (12)	6 (27)	0.17
Diabetes mellitus	1 (5)	6 (14)	0.42	5 (12)	2 (9)	1.00
Neoplasia	8 (40)	1 (2)	<0.01	8 (20)	1 (5)	0.14
Surgery						
Coelioscopy/laparotomy	10 (50)/10 (50)	42 (98)/1 (2)	<0.01	31 (76)/10 (24)	21 (95)/1 (5)	0.08
Surgical intervention						
Bypass	8 (40)	43 (100)	<0.01	29 (71)	22 (100)	0.01
Partial hepatectomy	6 (30)	0 (0)	<0.01	6 (15)	0 (0)	0.08
Other	6 (30)	0 (0)	<0.01	6 (15)	0 (0)	0.08
CFZ to end of surgery (min)[a]	180 (144–270)	120 (105–135)	<0.01	135 (120–202)	120 (105–135)	0.01
Blood loss (L)[b]	0.1 (0–0.4)	0 (0–0)	<0.01	0 (0–0.1)	0 (0–0)	0.16
Fluids administered (L)[b]	2.0 (1.5–2.0)	2.0 (1.3–2.5)	0.65	2.0 (1.5–2.0)	2.0 (1.5–2.5)	0.10
Biological data						
Creatinine (mg/dL)	0.7 (0.6–1.0)	0.7 (0.7–0.9)	0.77	0.7 (0.6–0.8)	0.8 (0.7–0.9)	0.11
$CL_{Cr,24h}$ (mL/min)[c]	130 (96–162)	104 (70–153)	0.17	100 (69–147)	130 (95–178)	0.05
Albumin (g/L)[d]	3.8 (3.6–3.9)	4.1 (3.8–4.4)	0.03	4.0 (3.6–4.4)	4.0 (3.8–4.4)	0.49
Free fatty acids (mg/dL)[d]	0.76 ± 0.23	0.92 ± 0.23	0.04	0.85 ± 0.23	0.92 ± 0.30	0.32
α-1-Acid glycoprotein (g/L)[d]	88.8 ± 50.3	90.3 ± 22.0	0.89	87.3 ± 35.7	94.7 ± 24.2	0.45
Total proteins (g/L)[d]	61.4 ± 12.8	64.8 ± 7.3	0.24	63.0 ± 9.9	65.3 ± 7.9	0.42

CFZ, cefazolin; $CL_{Cr,24h}$, measured creatinine clearance with 24-h urine collection.
Data are presented as counts (%), median (interquartile range) or mean ± standard deviation.
[a] Time from initiation of CFZ infusion until wound closure.
[b] Volume of blood loss or fluids administered until 180 min after initiation of the CFZ infusion.
[c] 24-h urine collects were not collected in 5 patients, so data on $CL_{Cr,24h}$ is presented for 58 patients.
[d] These serum parameters were not measured in 14 patients, so data on albumin, free fatty acids, α-1-acid glycoprotein and total proteins are presented for 49 patients.

The adequacy of *f*CFZ serum concentrations at T_{180} and T_{240} for different BMI (<35 kg/m^2 and ≥35 kg/m^2) and TBW (<120 kg and ≥120 kg) groups was explored.

2.8.2. Factors associated with insufficient serum concentrations of unbound cefazolin

Possible factors associated with insufficient *f*CFZ concentrations at T_{180} and T_{240} were investigated, including age, sex, BMI, TBW, abdominal circumference, $CL_{Cr,24h}$, blood loss and quantity of fluid administered until T_{180}, type of surgery, and serum concentrations of albumin, total proteins, α-1-acid glycoprotein and free fatty acids.

2.8.3. Statistical analysis

Categorical variables are reported as proportions. Continuous variables with or without normal distribution are reported as the mean ± standard deviation and median (interquartile range), respectively. Results from patients with a BMI ≥ 35 kg/m^2 were compared with those from patients with a BMI < 35 kg/m^2, and results from patients weighing ≥120 kg were compared with those from patients weighing <120 kg. Categorical data were compared using the χ^2 test or Fisher's exact test as appropriate. Continuous variables with normal distribution were compared using Student's *t*-test [or analysis of variance (ANOVA) for repeated measures and post-hoc Bonferroni corrections], and variables without normal distribution were compared with the Mann–Whitney test. Receiver operating characteristic (ROC) curve analysis was performed to test the accuracy of BMI and TBW as proxies for identifying patients with insufficient *f*CFZ serum concentrations at T_{240}. Pearson's linear correlation coefficient was calculated when evaluating *f*CFZ at T_{240} as a function of TBW and BMI. All tests were two-sided and *P*-values of <0.05 were considered statistically significant.

2.8.4. Ethics

The PK study was approved by the Erasme Hospital Ethics Committee and by the Belgian regulatory agency. Written informed consent was obtained from all patients.

3. Results

A total of 69 patients were included in this study, of whom 6 patients were eventually excluded (4 because serum samples were not taken during surgery, 1 because of an unknown pregnancy

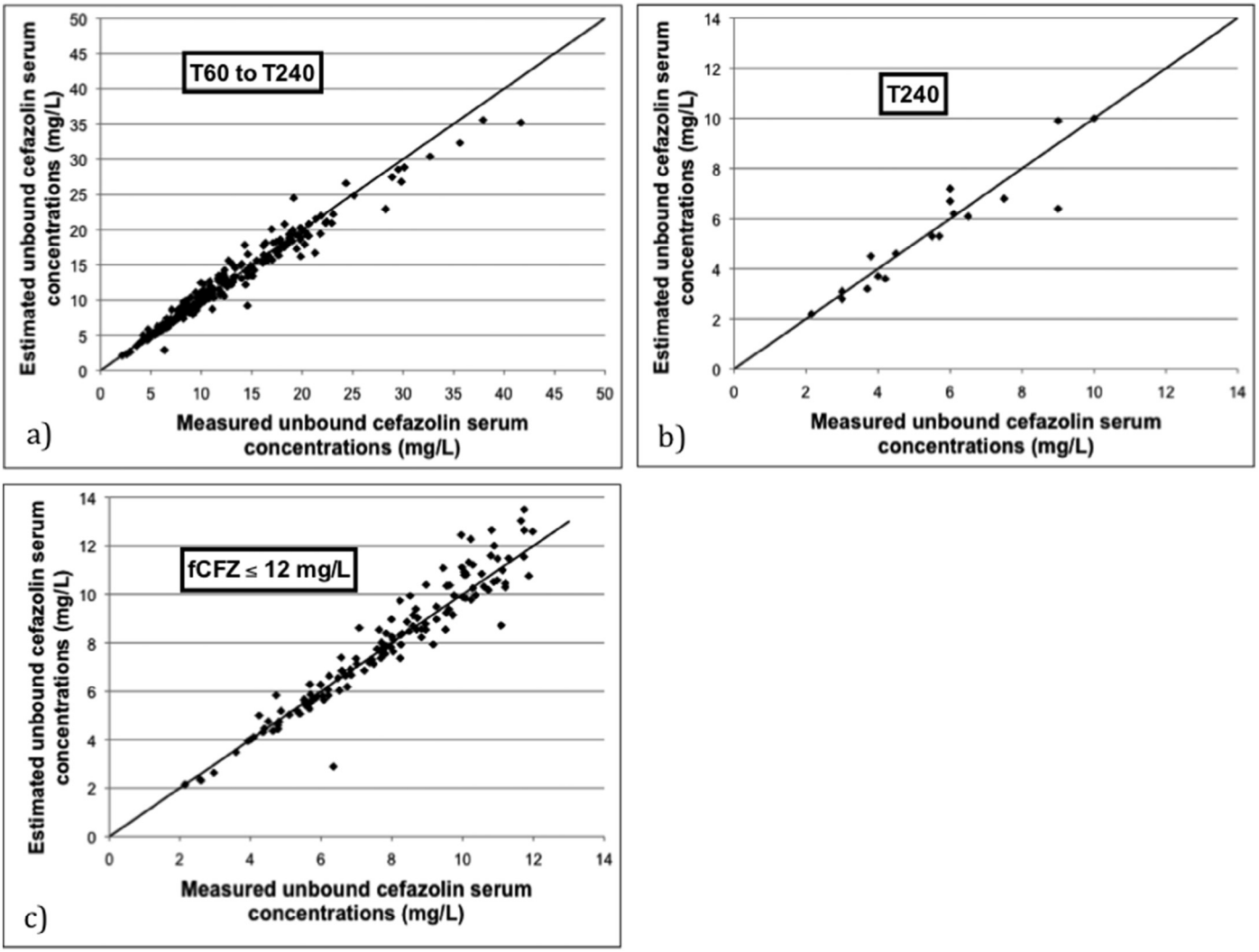

Fig. 1. Estimated unbound cefazolin (*f*CFZ) serum concentrations as a function of measured concentrations: (a) all measured serum samples taken from T_{60} until the end of sampling (n = 230 serum samples); (b) all measured samples at T_{240} (n = 17 serum samples; 17 patients); and (c) all measured samples with *f*CFZ serum concentration of <12 mg/L (n = 133 serum samples). Black solid line ($y = x$). T_{60}, serum sampling taken 60 min after the start of CFZ infusion.

diagnosed shortly after signing the informed consent and 1 because five of the seven serum samples showed marked haemolysis). At enrolment, the remaining 63 patients were stratified according to BMI (<30 kg/m^2, 12 patients; 30–39 kg/m^2, 21 patients; and ≥40 kg/m^2, 30 patients). For data analysis, patients were categorised according to BMI (<35 kg/m^2, 20 patients; and ≥35 kg/m^2, 43 patients) and TBW (<120 kg, 41 patients; and ≥120 kg, 22 patients). Twenty-four hour urine collections were not performed in 5 patients, and some serum parameters were not measured in 14 patients due to insufficient serum.

Patient characteristics, biological parameters and types of surgery are reported in Table 1. Most patients with a BMI ≥ 35 kg/m^2 or with a TBW ≥ 120 kg underwent laparoscopic gastric bypass surgery and none underwent partial hepatectomy. Only one post-operative SSI was reported. The majority of patients (56/63; 89%) were White Caucasians of European origin.

Because most of the surgical procedures lasted less than 240 min, serum samples were obtained in just 17 of the 63 patients at this time point. *f*CFZ serum concentrations were therefore estimated at T_{240} for the remaining patients as explained in Section 2.7. Fig. 1a shows the estimated *f*CFZ serum concentrations as a function of measured concentrations for the patients with measured *f*CFZ concentrations taken during the CFZ elimination phase (230 serum samples taken from T_{60} onwards); Fig. 1b shows the subgroup of 17 patients with concentrations measured at T_{240}; and Fig. 1c (133 serum samples) shows the subgroup of serum samples with a measured *f*CFZ serum concentration of <12 mg/L. The extrapolation method provided estimated *f*CFZ values that were not significantly different from measured *f*CFZ serum concentrations in any of these three groups (P = 0.20, 0.56 and 0.11, respectively). The estimated *f*CFZ concentrations at T_{240} for patients without measured serum *f*CFZ concentrations at this time point were therefore used for further analysis.

Fig. 2 illustrates *f*CFZ and *t*CFZ concentrations over time as a function of BMI and TBW. Independent of time, mean *t*CFZ and *f*CFZ serum concentrations were significantly lower in patients weighing ≥120 kg than in those weighing <120 kg (P = 0.01 and 0.01, respectively) but were not significantly different in patients with a BMI ≥ 35 kg/m^2 compared with those with a BMI < 35 kg/m^2 (P = 0.20 and 0.12, respectively). Furthermore, mean serum concentrations of *t*CFZ and *f*CFZ decreased significantly over time for both BMI and TBW groups. After post-hoc Bonferroni corrections, mean *t*CFZ and *f*CFZ differed significantly between T_{30}, T_{60}, T_{120} and T_{180}, but not between T_{180} and T_{240}.

Table 2 shows PK parameters of *t*CFZ and *f*CFZ in all study patients: the $AUC_{0–180}$ values were significantly smaller and the V_d was significantly greater in patients weighing ≥120 kg compared with those weighing <120 kg, but no differences were observed in the different BMI groups.

Fig. 3 shows adequate serum concentrations at T_{180} in all patients but in only 40/63 patients (63%) at T_{240}. No statistical differences were observed between the percentages of patients who had adequate *f*CFZ concentrations at T_{240} in the different BMI and TBW groups.

Fig. 4 shows serum concentrations of *f*CFZ at T_{240} as a function of BMI and TBW. No correlation was observed between BMI and *f*CFZ [r = –0.20, 95% confidence interval (CI) –0.43 to 0.05; P = 0.12] and a weak but significant negative correlation was observed between

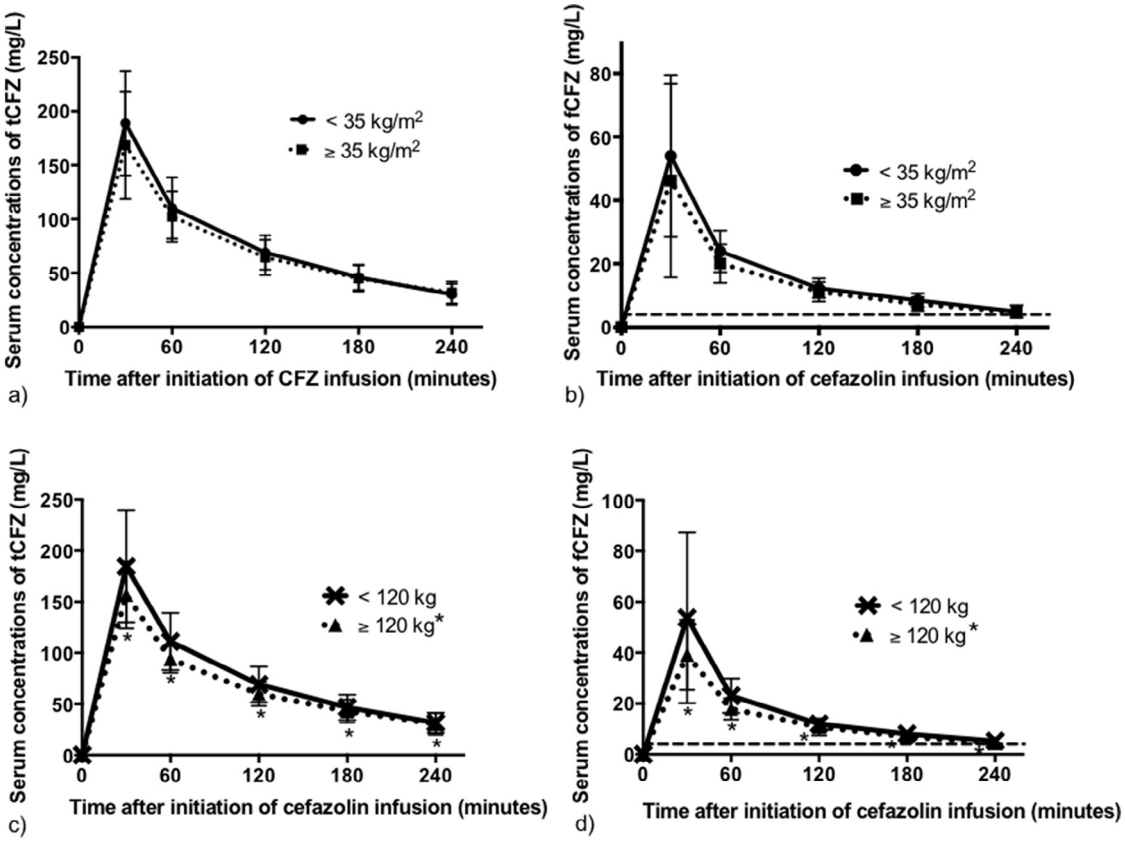

Fig. 2. Mean total cefazolin (*t*CFZ) and unbound cefazolin (*f*CFZ) serum concentrations over time as a function of body size: (a) *t*CFZ and (b) *f*CFZ as a function of BMI (<35 kg/m^2 vs. ≥35 kg/m^2); and (c) *t*CFZ and (d) *f*CFZ as a function of TBW (<120 kg vs. ≥120 kg). Results are presented as the mean ± standard deviation. Dashed horizontal black line = pharmacodynamic target of adequacy (4 mg/L). *P < 0.05 for the cohort with a TBW ≥ 120 kg compared with the cohort with a TBW < 120 kg. BMI, body mass index; TBW, total body weight.

Table 2
Pharmacokinetic (PK) parameters of unbound (free) cefazolin (*f*CFZ) and total cefazolin (*t*CFZ) in patients according to body mass index (BMI) and total body weight (TBW).

PK parameters	BMI			TBW		
	<35 kg/m^2 (n = 20)	≥35 kg/m^2 (n = 43)	P-value	<120 kg (n = 41)	≥120 kg (n = 22)	P-value
AUC_{0-180} (mg · h/L)						
*t*CFZ	306 (266–355)	278 (238–315)	0.08	307 (255–354)	260 (230–280)	<0.01
*f*CFZ	66 (55–80)	58 (51–67)	0.09	62 (55–74)	53 (49–61)	0.01
CL (L/h)						
*t*CFZ	5.1 ± 1.5	5.0 ± 1.1	0.90	5.0 ± 1.4	5.2 ± 1.0	0.50
*f*CFZ	24.5 ± 5.9	26.9 ± 7.2	0.19	25.1 ± 6.6	28.1 ± 7.1	0.10
V_d (L)						
*t*CFZ	11.9 ± 5.1	12.6 ± 2.9	0.50	11.7 ± 3.9	13.7 ± 3.0	0.04
*f*CFZ	51.0 ± 20.5	55.5 ± 27.4	0.52	48.6 ± 17.4	64.0 ± 34.1	0.02
$t_{1/2}$ (h)						
*t*CFZ	1.4 (1.2–1.8)	1.6 (1.3–1.8)	0.25	1.4 (1.2–1.7)	1.7 (1.2–2.1)	0.14
*f*CFZ	1.1 (1.0–1.6)	1.1 (0.9–1.4)	0.23	1.0 (0.9–1.4)	1.2 (0.9–1.6)	0.40

Data are expressed as the mean ± standard deviation or the median (interquartile range).
AUC_{0-180}, area under the concentration–time curve from 0–180 min; CL, total body clearance; V_d, volume of distribution; $t_{1/2}$, terminal elimination half-life.

TBW and *f*CFZ (r = –0.27, 95% CI –0.49 to –0.03; P = 0.03). No obvious cut-off point for adequate *f*CFZ serum concentrations could be identified for TBW or BMI.

In ROC curve analysis, a test that will not perform any better than chance will have an AUC value of 0.5. Both BMI and TBW performed poorly for detecting individuals who would benefit from an increased CFZ dosage regimen, with AUCs of 0.55 (95% CI 0.40–0.70; P = 0.54) for BMI and 0.57 (95% CI 0.42–0.72; P = 0.36) for TBW.

No factors were identified that were significantly associated with insufficient *f*CFZ at T_{240} (Table 3).

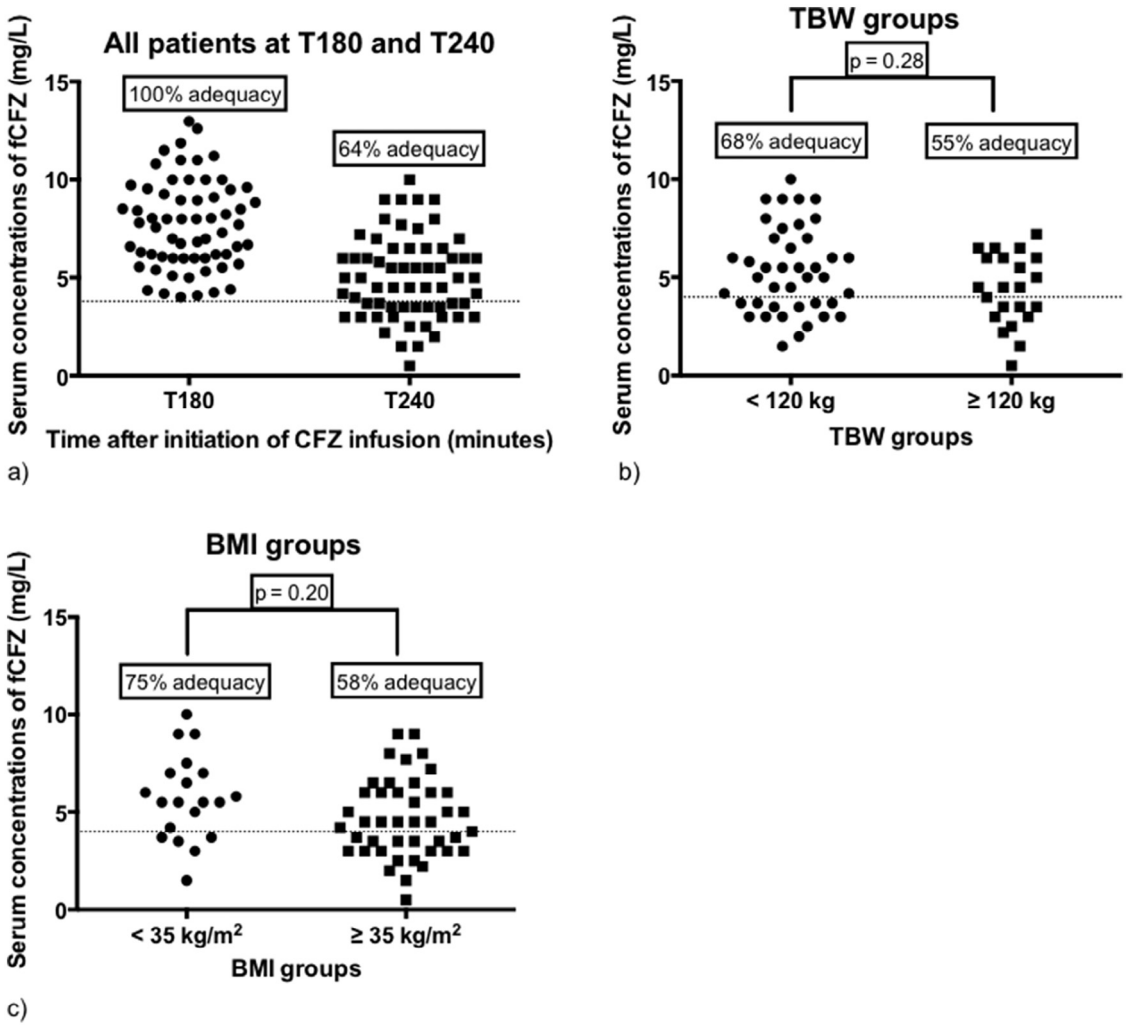

Fig. 3. Percentage of adequate unbound cefazolin (*f*CFZ) concentrations as a function of (a) timing of serum samples (in all patients at T_{180} and T_{240}), (b) TBW (<120 kg and ≥120 kg at T_{240}) and (c) BMI (<35 kg/m^2 and ≥35 kg/m^2 at T_{240}). Dashed horizontal black line = pharmacodynamic target of adequacy (4 mg/L). T_{180}, serum sampling taken 180 min after the start of CFZ infusion; T_{240}, serum sampling taken 240 min after the start of CFZ infusion; TBW, total body weight; BMI, body mass index.

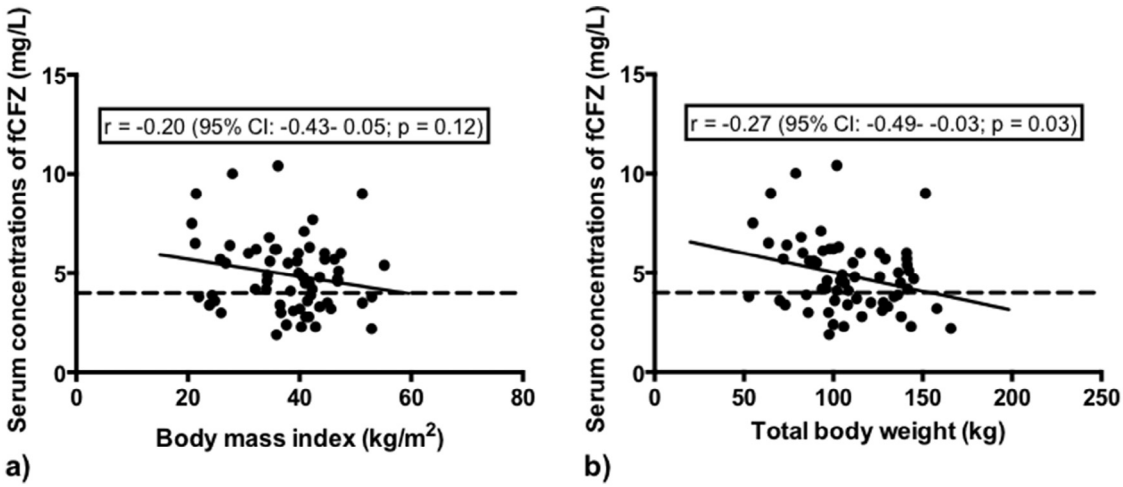

Fig. 4. Unbound cefazolin (*f*CFZ) serum concentrations at T_{240} as a function of (a) body mass index and (b) total body weight. Dashed horizontal black line = pharmacodynamic target of adequacy (4 mg/L); solid black line = Pearson linear correlation. *r*, Pearson's linear correlation coefficient; CI, confidence interval. T_{240}, serum sampling taken 240 min after the start of CFZ infusion.

4. Discussion

In this study, the accuracy of the recommended BMI (≥35 kg/m^2) and weight (≥120 kg) cut-offs proposed by the SPILF, SFAR and IDSA for increasing the CFZ dosage regimen for surgical prophylaxis was evaluated in a large cohort of essentially European Caucasian surgical patients. All patients had adequate serum concentrations at T_{180} but only two-thirds of patients at T_{240}. Despite a weak negative correlation between TBW and *f*CFZ serum concentrations at T_{240}, no significant differences in the percentage of patients with adequate *f*CFZ concentrations at T_{240} were observed in the different BMI and TBW groups. The BMI and TBW cut-offs proposed by the SFAR, SPILF and IDSA could not accurately identify which patients required higher CFZ dosage regimens to ensure adequate surgical prophylaxis until T_{240}. Moreover, no factors associated with insufficient *f*CFZ serum concentrations were identified in this cohort of patients.

This study confirms that 2 g of CFZ provided inadequate surgical prophylaxis for heavier patients, regardless of the criteria used (BMI ≥ 35 kg/m^2 or TBW ≥ 120 kg), for surgery lasting longer than 180 min. Even among the lighter patients, 2 g of CFZ also provided inadequate prophylaxis for surgery lasting longer than 180 min: only 75% of patients with a BMI < 35 kg/m^2 and 68% of patients weighing <120 kg had adequate *f*CFZ serum concentrations at T_{240}.

PK parameters were also only slightly different in the different TBW groups and were no different in the various BMI groups. Indeed, the AUC_{0-180} was smaller and the V_d was greater in patients weighing ≥120 kg compared with those weighing <120 kg. These data confirm observations already made in the literature in which TBW was identified as a covariate for the central V_d of CFZ [12,17,29]. We also found that values of V_d and CL for CFZ in patients weighing <120 kg and with a BMI < 35 kg/m^2 were greater than those reported in the literature in healthy non-obese patients [30–32]. This relatively large, heterogeneous cohort of patients may have captured the great variability of CFZ pharmacokinetics in today's surgical patients, supporting the notion that 'no one dose fits all'. Finding one dose that takes into account all potential factors that may influence the pharmacokinetics of an antibiotic, such as age, sex, body size, ethnic origin and more, is indeed difficult.

Table 3
Factors associated with insufficient serum concentrations of unbound (free) cefazolin (*f*CFZ) in all patients at 240 min after the start of cefazolin infusion.

Variable	*f*CFZ concentration <4 mg/L	*f*CFZ concentration ≥4 mg/L	*P*-value
No. of patients	23	40	
Age (years)	43 ± 12	47 ± 11	0.11
Male sex	6 (26)	11 (28)	0.90
TBW (kg)	113 ± 28	106 ± 25	0.24
BMI (kg/m^2)	39 ± 9	38 ± 8	0.40
Abdominal circumference (cm)	124 ± 19 (*n* = 20)	118 ± 17 (*n* = 35)	0.25
$CL_{Cr,24h}$ (mL/min)[a]	131 (87–164) (*n* = 20)	105 (75–147) (*n* = 38)	0.14
Free fatty acids (mg/dL)[b]	0.86 ± 0.34 (*n* = 17)	0.89 ± 0.19 (*n* = 32)	0.72
α-1-Acid glycoprotein (g/L)[b]	92.6 ± 25.4 (*n* = 17)	88.2 ± 35.7 (*n* = 32)	0.65
Albumin (g/L)[b]	40.0 ± 6.1 (*n* = 17)	39.2 ± 5.6 (*n* = 32)	0.64
Total proteins (g/L)[b]	64.3 ± 8.4 (*n* = 17)	63.5 ± 9.7 (*n* = 32)	0.76
Laparoscopy	19 (83)	33 (83)	0.99
Hepatectomy	2 (9)	4 (10)	0.87
Bypass	20 (87)	31 (78)	0.36
Blood loss[c]	1 (4)	4 (10)	0.44
Fluids administered[d]	9 (39)	9 (23)	0.16

TBW, total body weight; BMI, body mass index; *n*, total number of patients for whom results were available; $CL_{Cr,24h}$, creatinine clearance measured with 24-h urine collects. Data are presented as counts (percentage), median (interquartile range) or mean ± standard deviation.

[a] 24-h urine collects were not collected in 5 patients, so data on $CL_{Cr,24h}$ are presented for 58 patients.

[b] These serum parameters were not measured in 14 patients, so data on albumin, free fatty acids, α-1-acid glycoprotein and total proteins are presented for 49 patients.

[c] Blood loss >500 mL at 180 min after initiation of the cefazolin infusion.

[d] Volume of fluids administered >2500 mL at 180 min after initiation of the cefazolin infusion.

With only one SSI in this cohort, no conclusions could be made regarding the clinical impact of inadequate *f*CFZ serum concentrations. The only randomised controlled trials found in the literature comparing 2 g versus 3 g [33–35] or 4 g [36] of CFZ were conducted in obese patients undergoing caesarean sections, showing no clinical benefit for the higher dosage regimens despite significantly higher serum and tissue concentrations of CFZ [33–36].

This study has some limitations. First, the patient cohort was not extremely obese. However, the patient population was representative of the obese population in European countries and was heavy enough to test the recommended BMI and TBW cut-offs. Second, different patients in the cohort underwent different types of surgery, possibly influencing the pharmacokinetics of CFZ, independent of body size. However, current recommendations on CFZ dosing for surgical prophylaxis do not make distinctions between types of surgery, except when extracorporeal circulation is planned [7], and most patients in this cohort underwent minimally invasive surgery with minimal blood loss. Third, serum sampling was short and inadequacy of *f*CFZ was only observed at T_{240}, when most *f*CFZ values were estimated and not measured, therefore limiting the capacity to make robust conclusions regarding inadequate dosing. Fourth, use of the trapezoidal method in the PK analysis may have overestimated the AUC of CFZ. Fifth, despite a cohort of 63 patients, the sample size may still have been too small to detect significant changes in population groups. Finally, we did not measure tissue concentrations of CFZ, but only *f*CFZ serum concentrations.

In conclusion, this study has shown that 2 g of i.v. CFZ is insufficient to ensure adequate *f*CFZ concentrations for a large proportion of Caucasian European patients undergoing surgery lasting longer than 180 min. We need to find better predictors than BMI and TBW to identify which patients would benefit from an increased or modified CFZ dosage regimen to ensure adequate surgical prophylaxis.

Funding: None.

Competing interests: None declared.

Ethical approval: Ethical approval was given by the Ethics Committee of Erasme Hospital (Brussels, Belgium) [registration no. P2011/251] and the study was approved by the Belgian regulatory agency [2011-004070-29]. Written informed consent was obtained from all patients.

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