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CLINICAL REPORT

Cefepime Dosing in the Morbidly Obese Patient Population

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Abstract Proper dosing of specific antibiotics in morbidly obese patients has been studied inadequately. However, these data are beneficial as this patient population is at an increased risk to develop postoperative infections. Cefepime is an antibiotic used for the treatment of both gram-positive and especially gram-negative infections; administration of the appropriate dose in the morbidly obese population is crucial. We therefore examined the pharmacokinetics of cefepime in patients with body mass index >40 kg/m^2. Ten morbidly obese patients, with a mean [±SD] estimated glomerular filtration rate of 108.4±34.6 mL/min, undergoing elective weight loss surgical procedures were administered cefepime in addition to standard prophylactic cefazolin and studied. Serial serum cefepime concentrations were analyzed after dosing using a validated high performance liquid chromatography method. Pharmacokinetics and duration above the minimum inhibitory concentration (MIC) were determined using a protein binding value of 15% and a MIC threshold of 8 μg/mL. Mean free cefepime concentrations for t=30, 120, and 360 min were 69.6, 31.6, and 9.2 μg/mL, respectively. The dosing interval was calculated to maintain the free concentration above the MIC (fT > MIC) for 60% of the interval. This was determined to be 10.12 h, including time for infusion. There was no toxicity. Based on this analysis, an increased dose of 2 g every 8 h is necessary to maintain an adequate fT > MIC throughout the dosing interval. Further studies are necessary to determine the efficacy of this regimen in the settings of active infections and critical illness.

Keywords Antibiotics · Cefepime · Obesity · Pharmacokinetics

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Introduction

Obesity is an international pandemic, recognized by the World Health Organization (WHO) to affect nations across all socioeconomic levels [1]. Four hundred million people worldwide were obese (defined as body mass index (BMI) > 30 kg/m^2) in 2005, and the WHO estimates that 700 million people will be obese by 2015 [1]. The abundance of patients in this population leads to an increased number of obese patients requiring surgical procedures. This has a huge impact on health care, as patients in this population have an increased risk of surgical morbidity and mortality. Inevitably, increased pervasiveness of morbid obesity leads to increases in the numbers of critically ill obese patients, specifically those with infection. Obesity has been reported to be an independent risk factor for postoperative nosocomial infections [2, 3] including surgical site infections (SSI) [4–9].

Appropriate antimicrobial therapy for patients with postoperative infections is essential, as mortality rates, resistance rates, and length of hospital stay all increase when proper treatment is delayed or mistargeted [10]. Inappropriate dosing can also lead to a variety of complications, including inability

to eradicate bacteria and emergence of multi-drug-resistant bacteria, whereas overdosing and emergence of superinfections can lead to undesirable toxicities. It has been proposed that one factor leading to the increased SSI risk in obese patients is inappropriate low dosage, leading to decreased serum and tissue concentrations of prophylactic antibiotics [11]. Obesity alters physiologic parameters, making it more difficult to apply standard antimicrobial pharmacodynamics. For example, the increased glomerular filtration rate (GFR) observed in this population can increase clearance of renally excreted drugs [12]. Furthermore, a higher adipose/lean body mass ratio alters the volume of distribution (V_d) of both lipophilic and hydrophilic drugs [13]. The V_d of cephalosporins in obese patients is increased when compared to normal BMI controls, correlating with body surface area (BSA). Therefore, BSA should be considered when treating morbidly obese patients [14, 15]. Appropriate antibiotic dosing for morbidly obese patients remains inadequately studied. Data are most available for antibiotics that necessitate clinical monitoring of serum concentrations, such as aminoglycosides and vancomycin [16, 17]. Improved understanding of suitable dosing of additional antibiotics in obese patients will impact treatment and may decrease the morbidity and mortality in this high-risk population.

Cephalosporins are used commonly for antimicrobial therapy of critically ill patients. They are hydrophilic drugs with limited solubility in adipose tissue and are dosed based on the duration that the drugs' free concentrations are above the minimum inhibitory concentration ($T > MIC$). Cephalosporins are deemed efficacious when the free $T > MIC$ ($fT > MIC$) exceeds 60–70% of the dosing interval [18]. Cefepime is a frequently used, broad spectrum, fourth-generation cephalosporin with common use in the intensive care unit setting. However, its use has not been elucidated in the morbidly obese patient population. We therefore studied prospectively the use of cefepime in ten morbidly obese patients to determine an optimal dosing regimen in this patient population. We hypothesized that conventional dosing of cefepime (1–2 g IV q12 h) would be inadequate and would underdose patients in this population.

Materials and Methods

The study protocol was reviewed and approved by the Committee on Human Rights in Research of Weill Cornell Medical College (Protocol # 0903010298). Ten patients with a BMI > 40 kg/m^2 undergoing surgical procedures for morbid obesity (including Roux-en-Y gastric bypass, sleeve gastrectomy, and gastric banding) were enrolled as per institutional informed consent guidelines. Patients with an allergy to penicillins or cephalosporins, current pregnancy or lactation, chronic kidney disease, or chronic hepatic insufficiency were excluded.

Two grams of intravenous (IV) cefepime was infused over 30 min intravenously in the operating room prior to a bariatric procedure. Cefepime was given in addition to the prophylactic antibiotics given, comprising cefazolin with or without metronidazole. Serum concentrations of cefepime were assayed at 30, 120, and 360 min after intravenous infusion. Upon collection, the blood samples were allowed to clot for 10 min and centrifuged at 3,200 rpm for 10 min to separate serum. The serum was stored immediately at −80°C until analysis. All cefepime concentrations were determined using a previously validated high performance liquid chromatography method at the Center for Anti-Infective Research and Development (Hartford, CT, USA) [19]. Intra-day coefficients of variation for the low (2 mg/L) and high (40 mg/L) quality control samples were 2.74% and 5.39%, respectively. Inter-day coefficients of variation for the low and high quality control samples were 3.35% and 2.40%, respectively.

Total cefepime concentrations were analyzed for each individual subject by noncompartmental methods using WinNonlin 5.2 (Pharsight, Mountain View, CA, USA). The area under the concentration–time profile from $T=0$ to infinity (AUC_{inf}) was calculated using the linear trapezoidal method. The half-life ($t_{½}$) was calculated as $\ln(2) / K_e$, where K_e is the terminal elimination rate constant. The terminal elimination rate constant was estimated by linear regression analysis of the terminal portion of the concentration–time profile. Clearance was calculated as dose/AUC_{inf}. The V_d was calculated as dose / ($K_e \times AUC_{inf}$). These parameters were then used to estimate individual cefepime concentrations over 12 h and determine $T > MIC$. The $T > MIC$ was calculated using a protein binding value of 15%. A target $fT > MIC$ of 60% was used to determine the dosing interval using the susceptibility breakpoint MIC of 8 μg/mL, typical of gram-negative pathogens causing infections after elective surgery. Estimated GFR was calculated using the modification of diet in renal disease equation for GFR estimation [20].

Results

Demographic and preoperative data are presented in Table 1. There were five female and five male patients. The median age of this cohort was 39 years (range 31–74 years). Forty percent of patients were African-American, 40% were Hispanic, and 20% were Caucasian. Operations performed included two laparoscopic Roux-en-Y gastric bypass procedures, four laparoscopic placements of adjustable gastric band devices, and four laparoscopic sleeve gastrectomies. The mean [±SD] BMI was 48.43±5.29 kg/m^2, the mean serum creatinine was 0.8±0.2 mg/dL, and the mean estimated GFR (eGFR) was 108.4±34.6 mL/min.

Table 1 Patient characteristics

Patient	Age (years)/sex	Race	Body mass (kg)	BMI (kg/m^2)	sCr (mg/dL)	eGFR (mL/min)	Operation
1	34 F	Hispanic	125.6	47.55	0.9	77.1	LSG
2	74 M	Caucasian	135.6	48.26	1.1	69.5	LSG
3	34 F	African-American	106.8	41.37	0.6	147.4	LGB
4	31 F	Caucasian	130.2	49.75	0.6	123.9	LGB
5	35 M	African-American	139.3	40.55	0.9	123.7	LGB
6	43 F	African-American	138.6	56.81	0.5	173.5	LRYGB
7	48 F	African-American	143.6	53.00	0.9	86.1	LRYGB
8	61 M	Caucasian	163.2	54.00	1.1	80.7	LSG
9	55 M	Hispanic	160.0	48.52	1.0	82.5	LSG
10	32 M	Caucasian	151.0	44.52	0.8	119.1	LGB
Mean	45	–	139.4	48.43	0.8	108.4	–
SD	15	–	16.7	5.29	0.2	34.6	–

Demographics, preoperative data, and operation listed for each patient

F female, *M* male, *LSG* laparoscopic sleeve gastrectomy, *LGB* laparoscopic gastric band placement, *LRYGB* laparoscopic Roux-en-Y gastric bypass, *BMI* body mass index, *sCr* serum creatinine concentration, *eGFR* estimated glomerular filtration rate, *SD* standard deviation

Pharmacokinetic parameters were determined for each patient, as summarized in Table 2. The mean maximum concentration (C_{max}) was 81.8±25.9 μg/mL (range 42–131 μg/mL). The mean AUC_{inf} was 234.21±57.65 μg h/mL (range 137.81–322.44 μg h/mL). The mean clearance (Cl) for these ten patients was 9.09±2.58 L/h (range 6.20–14.51 L/h), whereas the K_e was 0.38±0.08 L/h (range 0.24–0.55 L/h). The mean half-life for 2 g cefepime was 1.92±0.42 h (range 1.26–2.80 h). The mean V_z was 24.59±6.79 L (range 15.49–38.05 L).

Mean cefepime concentrations (microgram per milliliter) for t=30, 120, and 360 min were 81.8±25.9, 37.2±7.0, and 10.9±4.7 μg/mL, respectively. The free cefepime concentrations were 69.6, 31.6, and 9.2 μg/mL, respectively. Individual free cefepime concentrations are listed in Table 2 and concentration–time profiles for each individual patient are shown in Fig. 1.

Using the mean pharmacokinetic parameters and a MIC ≤ 8 μg/mL (the susceptibility breakpoint for common gram-negative bacilli), dosing intervals were determined. To maintain ≥60% fT > MIC, the dosing interval (including time for infusion) was 10.12 h. The individual patient's dosing intervals are illustrated in Table 3.

Using the mean K_e, the mean cefepime concentrations, and 15% protein binding (assuming 80–90% fraction unbound), the fT > MIC was then determined for two dosing interval regimens, every 12 h and every 8 h, for MIC ranging from 0.0625 to 128 μg/mL. Table 4 summarizes these results and displays that a dosing interval of 8 h would give a fT > MIC greater than 60% for a MIC of 8 μg/mL,

Table 2 Individual patient pharmacokinetic parameters

Subject	C_{max} (μg/mL)	AUC_{inf} (μg h/mL)	Cl (L/h)	K_e (L/h)	$t_{½}$ (h)	V_z (L)
1	75.8	268.89	7.44	0.33	2.09	22.48
2	72.5	304.22	6.57	0.24	2.85	27.00
3	83.7	241.70	8.27	0.37	1.85	22.10
4	79.1	251.63	7.95	0.34	2.02	23.18
5	52.7	137.81	14.51	0.43	1.60	33.43
6	79.2	209.56	9.54	0.41	1.71	23.51
7	42.6	162.65	12.30	0.32	2.15	38.05
8	87.8	208.79	9.58	0.41	1.69	23.29
9	131.2	322.44	6.20	0.36	1.94	17.40
10	114.0	234.36	8.53	0.55	1.26	15.49
Mean	81.8	234.21	9.09	0.38	1.92	24.59
SD	25.9	57.65	2.58	0.08	0.42	6.79

Individual PK parameters: noncompartmental analysis by WinNonlin 5.2 (Pharsight Mountain View, CA, USA), C_{max} maximum concentration, AUC_{inf} area under the concentration–time profile from T=0 to infinity, Cl clearance, K_e terminal elimination rate constant, $t_{½}$ half life, V_z volume of distribution, *SD* standard deviation

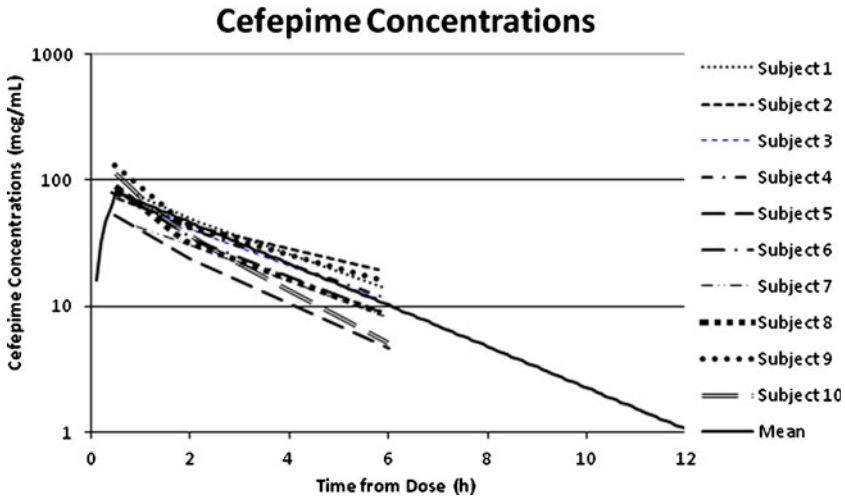

Fig. 1 This graph shows the concentration–time profiles for each patient and the mean of all patients

whereas a 12-h dosing interval would only give a *f*T > MIC of 51.7% for a MIC of 8 μg/mL.

Discussion

This study examines the administration of an antibacterial agent in the morbidly obese patient population. We specifically examined the use of cefepime, a fourth-generation cephalosporin, that is used widely for the treatment of both gram-negative and some gram-positive infections. Our results show that an increased dose of 2 g every 8 h should be used in this patient population to provide adequate therapy.

The prevalence of morbid obesity is increasing worldwide and has become a primary public health concern throughout the USA. Consequently, the use of bariatric surgery is increasing, with recent reports describing a tenfold increase in the number of bariatric operations completed in the USA from 1994 to 2005 [8]. Morbid obesity is a well-described risk factor for postoperative infectious complications [2–9]. Both Choban et al. and Canturk et al. described a significantly greater postoperative nosocomial infection rate in obese patients than the normal weight group [2, 3]. One recent multi-center prospective trial described a 7.9% overall rate of SSI after gastric bypass surgery [21]. The rate of SSI in obese patients after bariatric surgery is comparable to that observed for obese patients after nonbariatric surgery, with one study reporting a 15% SSI rate in both groups [22]. This not only influences patient outcome, but it affects overall health care cost as postoperative infections increase length of

Table 3 Cefepime concentrations

Patient	*f*[cefepime] (μg/mL) 30 min	*f*[cefepime] (μg/mL) 120 min	*f*[cefepime] (μg/mL) 360 min	100% *f*T > MIC[a] (h)	70% *f*T > MIC[a] (h)	60% *f*T > MIC[a] (h)	50% *f*T > MIC[a] (h)
1	64.40	40.37	12.06	7.36	10.3	11.93	14.21
2	61.63	36.97	16.55	9.07	12.74	14.78	17.63
3	71.12	32.64	9.84	6.61	9.22	10.68	12.71
4	67.22	35.45	9.58	7.03	9.83	11.38	13.56
5	44.81	20.06	3.92	4.81	6.66	7.69	9.13
6	67.28	28.28	7.78	5.98	8.33	9.63	11.46
7	36.17	26.92	7.23	5.89	8.21	9.49	11.29
8	74.61	28.08	7.59	5.93	8.26	9.55	11.36
9	111.51	36.24	13.44	7.58	10.62	12.31	14.67
10	96.90	31.21	4.32	5.29	7.35	8.49	10.09
Mean	69.56	31.62	9.23	6.27	8.75	10.12	12.05
SD	22.01	5.98	3.96	1.25	1.78	2.08	2.49

This table shows the *f*[cefepime] at each time point (30, 120, and 360 min). Additionally, the dosing intervals for each patient at 100% *f*T > MIC, 70% *f*T > MIC, 60% *f*T > MIC, and 50% *f*T > MIC

SD standard deviation, *f*T > *MIC* duration of time the free concentration is above the minimum inhibitory concentration

[a] MIC (minimum inhibitory concentration)≤8 μg/mL

Table 4 Dosing intervals using K_e

Dosing interval of 12 h												
MIC	0.0625	0.125	0.25	0.5	1	2	4	8	16	32	64	128
% fT > MIC	100.0	100.0	100.0	100.0	97.5	81.7	66.7	51.7	35.0	19.2	2.5	0.0
Dosing interval of 8 h												
MIC	0.0625	0.125	0.25	0.5	1	2	4	8	16	32	64	128
% fT > MIC	100.0	100.0	100.0	100.0	100.0	100.0	100.0	77.5	52.5	28.8	3.8	0.0

The table shows % fT > MIC for a range of MICs based on two dosing intervals, every 12 h and every 8 h

K_e terminal elimination rate constant, *MIC* minimum inhibitory concentration, % fT > MIC percent time free concentration is above the MIC

hospital stay, readmissions, intensive care unit admissions, and mortality. Furthermore, the treatment of SSI after bariatric surgery is no longer reimbursable [23]. Morbidly obese patients can experience up to a 6% risk of anastomotic leak after bariatric surgery; the incidence is even higher in revisional surgery [24–27]. In addition, there is a 9% rate of subcutaneous access port site infections [28]. Moreover, obesity is an independent risk factor for death in critically ill patients, and this may be due to a fourfold increase risk of nosocomial infection in this patient population [29]. Thus, the proper use of antimicrobial therapy in these settings is crucial to optimize patient outcomes and minimize morbidity and mortality.

Drug excretion, either by renal elimination or hepatic metabolism, is a fundamental element of pharmacokinetics. Cephalosporins, including cefepime, exemplify antibiotics that are excreted by the kidneys. In general, renal Cl can be influenced by perfusion, molecular size and charge, protein binding, and plasma oncotic pressure [30]. Hepatic metabolism, although not seen with cefepime, usually serves to solubilize drugs for eventual renal excretion. Antibiotics that are cleared hepatically may undergo enterohepatic circulation, which delays drug excretion. Therefore, malabsorption, cholestasis, and ileus may all affect antibiotic excretion [30] and not just when the agent is administered enterally. Specifically in morbid obesity, the pharmacokinetics of drugs are affected markedly; primarily, the V_d and Cl of drugs may be increased. Changes in Cl may be due to increased perfusion, blood volume, or organ size. These changes influence time-dependent antimicrobial therapies considerably, such as cephalosporins, as increases in V_d and Cl dictate higher dosages. For example, the V_d and Cl for cefamandole were increased in obese patients compared with normal BMI historical controls, requiring doubled doses to obtain similar concentrations [31]. Our results are consistent with that observation, as our patient cohort had an elevated V_d (24.6±6.8 vs. 16.6–19.3 L in a population of subjects whose weight was within 15% of the range of desirable height-adjusted weight) and an elevated Cl (9.1± 2.6 vs. 6.0–8.3 L/h in the aforementioned nonobese population). By contrast, the C_{max} and AUC_{inf} in our study cohort are comparable to historical controls, reinforcing that these parameters are not altered in morbidly obese patients [32].

Because of these changes, the proper usage of antimicrobial agents as surgical prophylaxis has been examined. Edmiston et al. proposed that perioperative prophylaxis using 2 g cefazolin may be unsuccessful in attaining sufficient concentrations in morbidly obese and super obese patients [11]. Similarly, Chen et al. concluded that obese patients likely require a greater dose of ertapenem than corresponding nonobese patients [33]. Additionally, Freeman et al. concluded that insufficient dosing of prophylactic vancomycin prior to bariatric surgery was a risk factor for SSI [34]. Ho et al. examined an optimal dosing regimen for cefazolin as a prophylactic antibiotic for surgery on morbidly obese patients and reported that 2 g of cefazolin is sufficient prophylaxis in general surgery, regardless of body mass [35]. However, there are limited data regarding the appropriate dosage of antimicrobials for treatment of postoperative surgical infections. Notably, no extant data describe proper dosing of cefepime in the morbidly obese population.

Cefepime is a broad spectrum, fourth-generation cephalosporin used for the treatment of complicated infections. Cefepime is not indicated for surgical prophylaxis, nor are we advocating its use therefore. The approved indications for its use are for febrile neutropenia, pneumonia, bacteremia, and urinary tract, abdominal, and skin or soft tissue infections [36–38]. It is used often to treat gram-negative infections, but it also has superior activity against certain gram-positive bacteria than many other cephalosporins, including methicillin-sensitive *Staphylococcus aureus* and *Streptococcus pneumoniae* [39]. Furthermore, cefepime is less susceptible to hydrolysis by beta-lactamases and may be less likely to induce resistance [40, 41]. It has been proposed that the use of cefepime increases mortality for unknown reasons, but hypothesized that perhaps inadequate antimicrobial efficacy is to blame [42]. This was not borne out in our own published experiences treating infections of critically ill patients [43]. Thus, studies determining the appropriate dosage and dosing interval in particular patient populations is crucial [44].

Cephalosporins exhibit time-dependent bacterial killing, such that they are most effective when free concentrations are sustained above the MIC for a particular period of time between doses. Cephalosporins have been reported to necessitate an $fT > MIC$ of 50–70% to treat gram-negative infections [45]. More specifically for cefepime, a $fT > MIC$ of 60% is associated with improved outcome [46]. According to the manufacturer guidelines for cefepime, a dose of 1 g every 12 h should be used for mild/moderate infections, 2 g every 12 h for severe infections, and 2 g every 8 h in neutropenic patients (all with a 30-min infusion time period). The latter is also the appropriate dose for patients with *Pseudomonas* infections [45]. A prolonged or continuous infusion of cefepime may also be beneficial in the critically ill patient; a 4-g/day continuous infusion is equivalent to a 2-g every 12-h dose (in combination with amikacin) with regards to duration of ventilation, duration of hospital stay, cure rate, and AUC/MIC of cefepime at 12 and 24 h. However, the $T > MIC$ was higher with the continuous infusion [45]. Using the Clinical and Laboratory Standards Institute-defined cut-off point of 8 μg/mL, a dosing interval to maintain ≥60% $fT > MIC$ is 10.12 h if administered by a 30-min infusion. We therefore recommend 2 g every 8 h for this patient population as well, when accounting for the potential of alterations in individual pharmacokinetics, the susceptibility of the pathogen, and the safety of cefepime. With this dosing interval, only one patient was slightly short of attaining ≥60% $fT > MIC$; however, this was only a one-time dose, and with continued dosing every 8 h, the serum concentration would increase after subsequent doses.

This study is not without limitations. The use of patients undergoing elective bariatric procedures and our exclusion criteria lead to a bias towards relatively healthy obese patients. The mean eGFR of these patients was relatively high, which also contributes to relatively increased clearance of medications undergoing renal metabolism and excretion. Additionally, we only gave one dose of cefepime to these patients, and a study examining pharmacokinetics while administering cefepime at 8-h dosing intervals or by continuous infusion would be valuable. Furthermore, serum concentrations of cefepime were determined; future studies should be completed examining the distribution, timing, and concentrations of the antibiotic within peripheral tissues. Lastly, this study has an adequate sample size for pharmacokinetic analysis; however, this sample size did not allow us to investigate infection or complication rates secondary to the use of cefepime.

Obese patients with postoperative surgical infections may benefit from increased dosing of cefepime. We recommend 2 g every 8 h to achieve adequate serum concentrations. A larger study looking at rates of infection using this dosage and rates of antibiotic-associated side effects or complications would be beneficial adjuncts to these data.

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Conflicts of Interest All authors declare no conflicts of interest or financial disclosures.

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