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Cefoxitin plasma and subcutaneous adipose tissue concentration in patients undergoing sleeve gastrectomy

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Abstract

Purpose—Antibiotic dosing in obese surgical patients has not been adequately evaluated. Cefoxitin is an antibiotic commonly utilized for surgical prophylaxis in cases involving the abdominal cavity. The objective of our study was to identify whether currently prescribed doses of cefoxitin achieve adequate and sustained plasma and tissue concentrations in obese patients undergoing sleeve gastrectomy

Methods—A prospective evaluation of plasma and tissue cefoxitin concentrations in patients undergoing sleeve gastrectomy was performed. On the day of surgical procedure, venous blood samples (5 mL) were collected just prior to cefoxitin administration and then at 5, 30, 60, 120, and

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The authors report no conflicts of interest.

240 minutes after dose administration. In addition subcutaneous adipose tissue was collected from the surgical site and the time of surgical incision and closure. Cefoxitin concentrations in the collected samples were quantified using HPLC – UV. A standard noncompartmental analysis was performed for each individual cefoxitin plasma concentration-time profile. In addition, the ratio of tissue to plasma concentration was calculated for all patients.

Findings—Plasma and tissue pharmacokinetics of cefoxitin were evaluated in 6 patients undergoing sleeve gastrectomy. At the time of surgical closure subcutaneous adipose tissue cefoxitin concentrations were subtherapeutic (< 8 mcg/mL) in all evaluated patients.

Implications—Current dosing strategies for cefoxitin in obese surgical patients may be inadequate and there is an urgent need to define the appropriate dosage.

Keywords

Cefoxitin; pharmacokinetics; obese surgical; bariatric; sleeve gastrectomy

Introduction

Obesity is a major public health concern, with more than 35.7% of adults in the United States classified as obese (defined as a body mass index (BMI) of ≥ 30 kg/m²). [1] Postoperative skin and soft structure infections (SSSIs) are responsible for roughly one quarter of the estimated 2 million healthcare associated infections annually. [2] Development of a SSSI is associated with significant morbidity and a mortality rate of 3%. [3] Data supporting the appropriate dosing of many antibiotics for perioperative prophylaxis in the obese population is lacking and often based on expert opinion rather than clinical evidence.

Cefoxitin is a second generation hydrophilic cephalosporin antibiotic with limited distribution in adipose tissue. [4] Cefoxitin covers a variety of aerobic and anaerobic gram positive and negative organisms. Bacterial killing of cefoxitin, as with other cephalosporins, is based on the duration of time that free concentrations are above the minimum inhibitory concentration ($T > MIC$). Optimally, the $T > MIC$ must exceed at least 60–70% of the dosing interval. [5] For prevention of post-operative infection it is ideal to exceed the MIC for the duration of the surgical procedure. The recommended dose of cefoxitin for surgical prophylaxis is 2 grams administered intravenously as a bolus. [6] Previous studies suggest that tissue concentrations of cefoxitin and other cephalosporins might be insufficient for providing antibiotic coverage in obese patients. [7, 8] The objective of our study was to identify whether currently prescribed doses of cefoxitin achieve adequate and sustained plasma and tissue concentrations in obese patients undergoing sleeve gastrectomy.

Materials and Methods

Study population and drug administration

The study protocol was approved by the Institutional Review Board. All subjects meeting inclusion criteria and consenting to participate received the institution standard cefoxitin therapy (2 grams as slow intravenous bolus over 5 minutes) just before induction of anesthesia in the operating room. Patients aged 18 to 65 years old undergoing elective sleeve

gastrectomy were eligible to participate. Patients with liver impairment (elevations in liver enzymes of greater than 3 times the upper limit of normal), reduced renal function (creatinine clearance < 50 mL/min), blood coagulation disorders, or anemia (hemoglobin < 12 mg/dL) were excluded from the study. All patients also received similar preoperative medications, which consisted of dexamethasone, famotidine, fentanyl, metoclopramide, and midazolam. Glomerular filtration rate (GFR) was estimated using serum creatinine (SCr) and cystatin C based equations.[9–11] SCr levels were extracted from the patient medical record on the day of the surgical procedure. Plasma cystatin C concentrations were obtained using a Quantikine ELISA kit (R&D Systems, Minneapolis, MN).

Sample Collection

Serial venous blood samples were drawn from an antecubital intravenous line opposite to the arm in which cefoxitin was infused. Venous blood samples (5 mL) were collected in EDTA K2 or K3 tubes just prior to cefoxitin administration and then at 5, 30, 60, 120, and 240 minutes after dose administration, and plasma was separated by centrifugation. Approximately 1 gram of subcutaneous adipose tissue was excised from the surgical site at the time of incision and at wound closure. Plasma and tissue samples were stored at –80°C until analysis.

Quantitation of Cefoxitin in Plasma and Adipose Tissue

Quantitation of cefoxitin was adapted from a previously published HPLC method.[12] The blank plasma used for the preparation of calibration standards was obtained from the New Brunswick affiliated hospital blood bank (New Brunswick, NJ). Human adipose tissue was purchased from Lee Biosolutions Inc. (Saint Louis, MO). Plasma samples and standards (100 µL) were spiked with 10 µL internal standard (cefotaxime sodium 100 µg/mL in methanol) and deproteinized with 400 µL acetonitrile. After centrifugation at 13,000 g for 10 min, the supernatant was evaporated to dryness. The residue was reconstituted in 200 µL of the mobile phase, and 50 µL was injected into the HPLC system. Adipose tissue samples were thawed and cut into the pieces about 100 mg for cefoxitin measurement. The tissue was immediately homogenized in 0.5 mL water for 5 minutes using Polytron PT 1300D homogenizer. For calibration standards, blank adipose tissue homogenate was spiked with known concentrations of cefoxitin and internal standard. The resulting tissue sample homogenates and calibration tissue standards were processed as described for plasma samples.

Chromatographic separation was completed using an ODS-AQTM column (5µm, 4.1 × 250 mm, YMC America Inc., PA) on a Waters HPLC system equipped with a 717plus autosampler, 486 tunable UV detector and Hitachi L-7100 pump. The mobile phase consisted of 100mM sodium acetate and acetonitrile (90:10, pH=4.5), and the flow rate was 0.8 mL/min. The detection wavelength was set at 254 nm. The retention times of cefoxitin and the internal standard were 11.6 minutes and 14.7 minutes. The calibration curves were linear between 3.9 to 500 µg/mL for plasma and 2.5 to 100 µg/g for adipose tissue. The acceptable absolute recovery of cefoxitin (85.4%) and internal standard (92.0%) was obtained for the method. Absolute recovery was calculated as the peak area ratio between the tissue homogenate and solvent standard.

Pharmacokinetic analysis

A standard noncompartmental analysis was performed for each individual cefoxitin plasma concentration-time profile using Phoenix WinNonlin 6.1 software (Pharsight, Mountain View, CA). Terminal half-life, area under the concentration-time curve from time zero to infinity (AUC, calculated by linear trapezoidal method), volume of distribution at steady state (V_{ss}), and systemic clearance (CL) were calculated. Individual plasma concentration-time profiles were evaluated using one compartment model. Plasma concentration at the time of wound closure was determined from the fitted profiles, and the ratio of tissue to plasma concentration was calculated for all patients.

Results

Six patients were enrolled and evaluated for single dose cefoxitin pharmacokinetics. Patient clinical and demographic data and calculated pharmacokinetic parameters are summarized in Table 1. At the time of incision, 4 of 6 patients had tissue cefoxitin concentrations above the MIC for anaerobes (16 mcg/mL) versus 5 of 6 patients had coverage for aerobic infections (8 mcg/mL). At the time of surgical closure, none of the patients enrolled in the study had maintained a therapeutic cefoxitin tissue concentration (Figure 1, defined as a tissue concentration of > 8 mcg/mL). Individual data profiles were fitted using one compartment model with first-order elimination and the volume of distribution and clearance were determined (19.47 ± 9.75 L and 15.25 ± 2.73 L/h, respectively). The ratio of tissue-to-plasma concentrations at the time of wound closure was 0.12 ± 0.03 . There was no correlation between estimated GFR (calculated using Cockcroft Gault and Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equations) and tissue concentration at the time of surgical closure.

Discussion

Cefoxitin pharmacokinetics in obese subject undergoing sleeve gastrectomy has not been evaluated before. *In vitro*, cefoxitin exhibits a MIC of 8 mcg/mL or less for aerobic organisms and 16 mcg/mL or less for anaerobic organisms.[13] Although we found that plasma cefoxitin concentrations exceeded the MIC for the duration of the sleeve gastrectomy procedure, this was not the case for subcutaneous adipose tissue. Tissue concentrations at the time of surgical incision were above an MIC of 8 mcg/mL for 5 of 6 patients. Reaching an adequate tissue concentration is essential at the time of incision to prevent infection; however, ideally antibiotic concentrations should remain above the desired MIC for the duration of the procedure for optimal benefit.[6,14,15] In all patients, the tissue concentration at the time of surgical closure was below an MIC of 8 mcg/mL. Several studies suggest a negative correlation between end of procedure tissue and serum concentrations of antibiotics and infection rate.[8,16,17] Of note, the mean procedure time was 78.2 ± 23.6 minutes which is less than the time where redosing of cefoxitin is advocated.[6] There was some variation in the initial plasma cefoxitin concentrations; however, the plasma concentration of a compound administered intravenously is expected to change rapidly within the first few minutes after administration due to the distribution processes. Some of the variability can therefore be attributed to the timing of the first

sample, which varied from 5 to 9 minutes. Relying on antibiotic plasma concentrations, as a metric for success is short sighted and does not assure adequate tissue levels throughout the dosing interval. Rather, tissue concentrations are more appropriate to identify the optimal dosing for infections involving the skin and soft structures. In order to optimize antibiotic dosing and choose the most effective therapies in the obese population, a better understanding of antibiotic tissue disposition is essential. Ultimately, optimization of dosing should reduce the occurrence of SSSI; an endpoint that requires a large sample to assess.

The majority of cefoxitin pharmacokinetic studies have included normal weight or healthy subjects with few data in obesity.[7,18,19] Typical cefoxitin plasma concentrations depending on renal function range from 14.3 mcg/mL to 86.0 mcg/mL (after a single dose of 30 mg/kg) at 2 hours post dose.[18] Peak cefoxitin concentrations after intravenous administration in healthy adults has been reported as 244 mcg/mL.[19]

Pharmacokinetic parameter values from the current study were compared to the reference data from Toma et al.[7] which evaluated cefoxitin in obese patients undergoing abdominal and pelvic surgery and normal weight subjects. In Figure 2; the mean concentration-time profile of cefoxitin in obese subjects from Toma et al.[7] is provided for comparison. Despite increased prophylactic doses of cefoxitin from 1 to 2 grams prior to surgery, obese patients enrolled in their study had inadequate cefoxitin tissue concentrations. Adipose tissue concentrations were 7.8 mcg/g and 2.7 mcg/g at incision and closure respectively. Of note, the time the tissue sample at closure was excised was at a mean of 2.4 hours post dose. By contrast, tissue sample at closure was excised at approximately a mean of 78 minutes post dose in the current study. Thus, an even a shorter surgery length was insufficient in maintaining tissue cefoxitin concentrations above the MIC at the time of closure.

Several pharmacokinetic parameters may be altered in the obese population as a result of altered volume of distribution, total body clearance, and plasma protein binding (alpha-1 acid glycoprotein).[20] In obesity, variation in blood flow within adipose tissue, cytochrome P-450 enzyme activity, and GFR may all contribute to altered pharmacokinetics and inadequate drug concentrations in target tissue.[21] Isla and colleagues performed a prospective study involving 56 patients undergoing colorectal surgery who received 2 grams of prophylactic cefoxitin to develop a population pharmacokinetic model.[22] They determined that in order to maintain adequate cefoxitin plasma concentrations, redosing would depend on renal function CrCl (redose at 1.5 hours if CrCl 60 – 80mL/min and at 1 hour if CrCl > 100 mL/min). This finding is intriguing, as obese patients often have augmented GFR.

Collectively, the literature on antibiotic dosing in obese surgical patients is scarce. The majority of available data supporting the use of higher antibiotic doses have evaluated cefazolin. In a small two-phase study evaluating 1 gram of prophylactic cefazolin administered prior to gastroplasty in morbidly obese adults, plasma and tissue cefazolin concentrations were lower in the obese patients compared to normal weight patients.[23] Furthermore, cefazolin concentrations did not surpass the MIC required to prevent infection in the morbidly obese patients. In the second phase of the study, the dosage was increased to 2 grams of prophylactic cefazolin. The dose increase resulted in adequate plasma and tissue

concentrations and a significant reduction in SSSIs (5.6% versus 16.5%; $p=0.03$) compared to patients in the first phase. Edmiston and colleagues evaluated perioperative cefazolin (2 grams) prophylaxis in 38 patients undergoing a Roux-en-Y gastric bypass procedure. Patients were stratified into three groups depending on BMI and both serum and tissue cefazolin concentrations were evaluated.[24] There was an inverse relationship between BMI and serum cefazolin concentration. Tissue concentrations were below the target level (8 mcg/mL) at all time points measured with the exception of the lowest BMI group at the time of closure. This finding is expected as cefazolin tissue distribution is lower in morbidly obese patients.[25] Toma and colleagues reported that the tissue distribution of cefoxitin are lower in obese patients.[7]

There were some limitations to our study including small sample, measurement of total cefoxitin concentration rather than free cefoxitin, and measurement of tissue concentrations at only 2 time points. If free cefoxitin concentrations were measured, they would be expected to be lower than total cefoxitin concentrations due to the binding of cefoxitin to plasma and cellular proteins and therefore strengthen our argument of the inadequacy of current cefoxitin dosing practices in obese patients. With regards to the limited time points of tissue sampling, this strategy was chosen due to the feasibility within the framework of surgical procedure and intended to provide minimal interference in clinical care. As a result, we are unable to determine the exact time point when the tissue concentrations became subtherapeutic. Despite these limitations, the intent of this study was to provide preliminary data to support a larger scale clinical study. Inadequate antibiotic concentrations may place patients at risk for treatment failure and allow bacteria to develop resistance. There is an urgent need to identify appropriate antibiotic dosing strategies in obese patients.

Future studies are needed to confirm whether a dosage increase would achieve adequate tissue concentrations. Furthermore, the impact and importance of duration of therapeutic concentration in tissue on rates of SSSI are still to be determined. Given the low postoperative infection rates in laparoscopic procedures, surrogate markers such as tissue concentrations at incision and closure are an important initial step to better understand appropriate doses in obese patients. These data also provide important insight on treatment of infections in obese patients.

Conclusion

Currently recommended doses of cefoxitin used for surgical prophylaxis in obese patients may not achieve therapeutic tissue levels through the duration of the surgical case and may predispose patients to surgical site infections. Additional studies are needed to confirm this hypothesis.

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Figure 1.

Cefoxitin subcutaneous adipose tissue concentrations at incision and closure in relation to minimum inhibitory concentration. Cefoxitin typically exhibits an MIC of 8 mcg/mL or less for aerobic organisms and 16 mcg/mL or less for anaerobic organisms.[13] Note: Only two time points were assessed; therefore, it is unknown when the cefoxitin concentration fell below 8 mcg/mL

Figure 2.
Comparison of observed plasma cefoxitin levels to historical data (Toma et al., [7] solid line) in obese patients.

Table 1

Patient Demographics and Pharmacokinetic Parameters.

Parameter	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6	Total Mean $\pm$ SD
Age (y)	57	48	51	45	52	39	48.7 $\pm$ 6.2
Female	Y	N	Y	Y	Y	Y	83.3% ^a
Race	White	White	Black	Black	White	White	66.7% ^b
Total body weight (kg)	107.8	99.4	103.6	111.2	105.0	157.5	114.1 $\pm$ 21.6
Ideal body weight (kg)	50.6	63.8	54.1	59.2	48.8	59.6	48.9 $\pm$ 5.87
Height (cm)	158	168	162	168	156	168	163.3 $\pm$ 5.4
BMI (kg/m ²)	43.2	35.4	39.5	39.4	43	56	42.8 $\pm$ 7.1
CrCl (ml/min) ^c	61.9	90.6	81.4	95.4	46.1	79.0	75.7 $\pm$ 18.5
CrCl (ml/min) ^d	82	82	111	111	87	91	94.0 $\pm$ 13.6
Procedure duration (min)	81	86	78	117	54	53	78.2 $\pm$ 23.6
AUC (h•mg/L)	235.4	203.8	157.3	150.7	111.4	77.5	156.0 $\pm$ 57.9
CL (L/h)	8.5	9.8	12.7	13.3	18.0	25.8	14.7 $\pm$ 6.4
V _{ss} (L)	17.2	17.9	11.6	13.4	20.1	33.3	18.9 $\pm$ 7.7
T _{1/2} (h)	1.4	1.3	0.7	0.9	0.9	1.0	1.0 $\pm$ 0.3

Note: Cefoxitin dosage = 2 grams over 5 minutes. Abbreviations: AUC=area under the curve, CL=clearance, V_{ss}=Volume of distribution at steady state, T_{1/2}=half-life. Values are presented as mean $\pm$ SD.

^a Percent female

^b Percent White

^c Estimated with Cockcroft-Gault Equation, SCr based

^d Estimated using the CKD-EPI Equation, cystatin-C based