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ORIGINAL CONTRIBUTIONS

Optimal Cefazolin Prophylactic Dosing for Bariatric Surgery: No Need for Higher Doses or Intraoperative Redosing

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Abstract
Purpose The goal of this pharmacokinetic (PK) study was to evaluate whether a single 2-g prophylactic dose of cefazolin given (IV) bolus provides effective protective cefazolin levels for prophylaxis against methicillin-sensitive *S. aureus* (MSSA), the primary skin pathogen in bariatric surgery.
Materials and Methods Thirty-seven patients having gastric bypass or sleeve gastrectomy received cefazolin 2-g preoperative prophylaxis. Serum, subcutaneous adipose tissue, and deep peri-gastric adipose tissue specimens were collected at incision and before skin closure. Cefazolin concentrations in serum and adipose tissue were determined by high-performance liquid chromatography.
Results Penetration of cefazolin, a water soluble antibiotic, into adipose tissue was only 6–8 % of simultaneous serum levels. However, cefazolin tissue concentrations in all adipose tissue specimens, exceeded mean MIC for MSSA.
Conclusions Prophylactic cefazolin, given as a single 2 g (IV bolus 3–5 min before skin incision) was more than adequate in providing protective cefazolin levels for the duration of bariatric surgery. Cefazolin 2 g (IV dose bolus given just before skin incision) achieves protective adipose tissue levels (> MIC of MSSA) for the duration (usually < 4 h) of bariatric surgical procedures. In this study, cefazolin 2 g (IV bolus) provided protective adipose tissue levels for 4.8 h. Since cefazolin is a water soluble antibiotic (V_d = 0.2 L/Kg), penetration into adipose tissue is not V_d not dose-dependent. Extremely high-dosed cefazolin, i.e., 3 or 4 g is excessive and unnecessary for bariatric surgery prophylaxis. A single cefazolin 2 g preoperative dose also eliminates the need for intraoperative redosing at 4 h.

Keywords Cefazolin pharmacokinetics · Surgical antibiotic prophylaxis · Antibiotic intraoperative redosing

Introduction

Bariatric surgery is an option for morbidly obese patients who have failed lifestyle modifications and pharmacotherapy. However, as with other surgical procedures, bariatric surgery has a risk of surgical site infections (SSIs), i.e., 1–21.7 % [1]. The most common and important SSI pathogen in bariatric surgery is *Staphylococcus aureus* (MSSA), and for this reason, cefazolin is the preferred antibiotic for bariatric surgery prophylaxis [2].

Cefazolin is highly active against the most common Gram positive SSI pathogens, e.g., methicillin-sensitive *S. aureus* (MSSA). For cefazolin, the mean minimum inhibitory concentration (MIC) for MSSA is 1 mg/L. Optimally, cefazolin is administered intravenously (IV) preoperatively by IV bolus over 3–5 min just before skin incision [3, 4]. Cefazolin is highly water soluble as indicated by its low volume of distribution (V_d = 0.2 L/kg), i.e., cefazolin is lipid insoluble. Cefazolin is 86 % protein bound and has a serum half-life ($t_{1/2}$) of 1.2–2.2 h in adults with normal renal function. For SSIs not involving

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adipose tissue, the usual therapeutic dose of cefazolin (in adults with normal renal function) is 1 g (IV) q 8 h [3, 5].

American Society of Health-system Pharmacists (ASHP) guidelines recommend prophylactic cefazolin 2 g (IV) to be administered within 60 min prior to surgery, and for procedures of long duration, i.e., > 4 h, cefazolin redosing at 4 h is suggested [2]. Because the penetration of cefazolin into adipose tissue is so poor, others have used cefazolin (IV) 3–4 g for pre-op prophylaxis in patients with body weight ≥ 120 kg. However, cefazolin pharmacokinetic data (PK) in the morbidly obese is limited [6]. After a cefazolin 1 g (IV) dose, in non-obese and obese adults, peak serum levels are ~ 185 mg/L, levels of > 4 mg/L persist for 8 h [3, 5]. Because cefazolin is water soluble (V_d = 0.2 L/kg), penetration into adipose tissue is poor, i.e., not dose-dependent, even with extremely high doses [6]. Because previous PK studies were small/varied in study designs, we conducted a PK study of cefazolin to prevent SSIs in bariatric surgery [7–10].

Pharmacodynamically (PD), effective protection is maintained during the entire dosing interval if ß-lactam levels > MIC are maintained for at least 60 % (4.8 h) of the dosing interval, i.e., q 8 h. The continued inhibition of susceptible pathogens when antibiotic levels drop to below the MIC (subtherapeutic) is known as the post-antibiotic effect (PAE). Cephalosporins have marked PAE with Gram-positive organisms, e.g., *S. aureus*. Therefore, if cefazolin levels (> MIC of *S. aureus*) are maintained for at least 60 % of the dosing interval (4.8 h), *S. aureus* remains inhibited during the remainder of the 8-h dosing interval [3–5]. This has important PK implications for the need, or lack thereof, for intraoperative redosing in bariatric surgery.

Materials and Methods

This was an open-labeled, unblinded prospective pharmacokinetic study approved by the IRB at Winthrop-University Hospital. The study recruited 37 patients undergoing Roux-en-Y gastric bypass (RYGB) or laparoscopic sleeve gastrectomy (LSG), aged 18–60 years old, with a body mass index (BMI) ≥ 35 kg/m^2. Patients were not preselected by the surgical service (obese vs extremely obese, i.e., > 200 kg). Patients who were pregnant, had moderate renal impairment (serum creatinine > 1.5 mg/dl), or were allergic to penicillin were excluded.

Standardized chlorhexidine preoperative skin preparation was the same for all patients. Patients received a single dose of cefazolin 2 g (IV push) 3–5 min before skin incision. The following samples were collected at the time of initial incision and before the skin closure. Blood samples were collected at the same time that tissue samples were collected. Blood samples were allowed to clot and then centrifuged at 3200 rpm for 10 min to separate the serum. The serum was aliquotted and frozen at −80 °C. Immediately after collection, the adipose tissue were rinsed with normal saline and blotted dry on sterile gauze. Each sample was placed in an individual specimen container, labeled and stored on wet ice until transported to storage at −80 °C. Cefazolin concentrations were determined using a validated high pressure liquid chromatography (HPLC) assay at the Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, CT. In addition, no port infections or SSIs occurred within 30 days of surgery for any patient (infections are required to be reported to the Department of Bariatric Surgery).

Results

Thirty-seven patients completed the study, 11 men (30 %) and 26 women (70 %). The mean age was 45 + 13 years old, mean weight was 127 + 29 kg, and mean BMI was 46 + 8 kg/m^2. The majority of the patients were Caucasian (92 %) while only three patients were African-American (8 %).

Table 1 Cefazolin concentration in serum, subcutaneous, and peri-gastric adipose tissue

	Time from cefazolin administration (minutes)	Mean cefazolin concentration (mg/L or mg/kg)
Samples at incision		
Serum	16 ± 5	159.96 + 57.8
Subcutaneous adipose tissue	16 ± 4	8.78 ± 5.11
Peri-gastric adipose tissue	15 ± 3	10.38 ± 5.44
Samples before closure by procedures		
Sleeve		
Serum	71 ± 23	119.85 ± 63.63
Subcutaneous adipose tissue	74 ± 21	6.93 ± 4.22
Peri-gastric adipose tissue	65 ± 26	6.15 ± 2.23
Sleeve + other procedures		
Serum	106 ± 44	101.53 ± 36.76
Subcutaneous adipose tissue	108 ± 40	6.08 ± 3.03
Peri-gastric adipose tissue	104 ± 43	9.66 ± 9.62
Gastric bypass		
Serum	159 ± 47	80.31 ± 21.23
Subcutaneous adipose tissue	167 ± 45	8.11 ± 4.35
Peri-gastric adipose tissue	163 ± 44	7.49 ± 3.77

This study included 30 (81 %) LSG and 7 (19 %) RYGB. During these surgeries, if needed, additional procedures were also performed during the procedure, e.g., removal of previous gastric banding, hernia repair, and liver biopsy. Sleeve gastrectomy is usually a short procedure, but additional procedures could prolong surgery duration. The mean duration for sleeve procedure was 90 + 24 min, for sleeve and other procedures was 128 + 50 min, and for gastric bypass was 177 + 39 min. None of these bariatric procedures lasted longer than 4 h.

The first set of samples was collected approximately 15 min after cefazolin administration, regardless of type of bariatric surgery. A second set of samples was collected at various times depending on the bariatric surgical procedures. (Table 1). The concentrations of cefazolin exceeded 1 mg/L (MIC of *S. aureus*) in virtually all samples. In subcutaneous and peri-gastric adipose tissue, cefazolin concentrations were approximately 6–8 % of simultaneous serum concentration. (Figs. 1a, b, c) No SSIs occurred within 30 days of surgery for any patients.

Conclusion

Cefazolin PK/PD parameters in morbidly obese patients have not been well characterized [6]. In this population, practice guidelines recommend weight based dosing using extremely high dose cefazolin, e.g., 3–4 g (IV infusion time unspecified), even though cefazolin is not lipid soluble, and clinical data to support is lacking [2].

Cefazolin, a ßeta-lactam antibiotic, displays time-dependent killing PK/PD characteristics. Antimicrobial activity of cefazolin related to the time above the MIC of the pathogen, i.e., MIC = 1 mg/L for *S. aureus* (MSSA) [5]. The antibacterial effect of cefazolin continues if levels > MIC are maintained for at least 60 % of the dosing interval (4.8 h) and persists during the remainder of the dosing interval (8 h). Susceptible organisms, e.g., MSSA remain inhibited for the remainder of the 8-h dosing interval (final 3.2 h) even after antibiotic levels become subtherapeutic (< 1 mg/L) due to the PAE [3, 4].

This PK study demonstrated that a single prophylactic dose of cefazolin 2 g (given IV bolus over 3–5 min before skin incision) provided protective cefazolin concentrations exceeding the MIC of *S. aureus* (MSSA) with a MIC < 1 mg/L in blood and adipose tissue for the duration of bariatric surgery, and indicated additional intraoperative cefazolin dosing is unnecessary.

The penetration of cefazolin (a water soluble antibiotic with a low V_D = 0.2 L/kg) predictably was only 6–8 % of simultaneous serum levels in adipose tissue. However, a cefazolin 2 g IV bolus (given over 3–5 min) just before skin incision provided optimal protective antibiotic concentrations >MIC of *S. aureus* (MSSA) in adipose tissue in obese patients undergoing bariatric surgery.

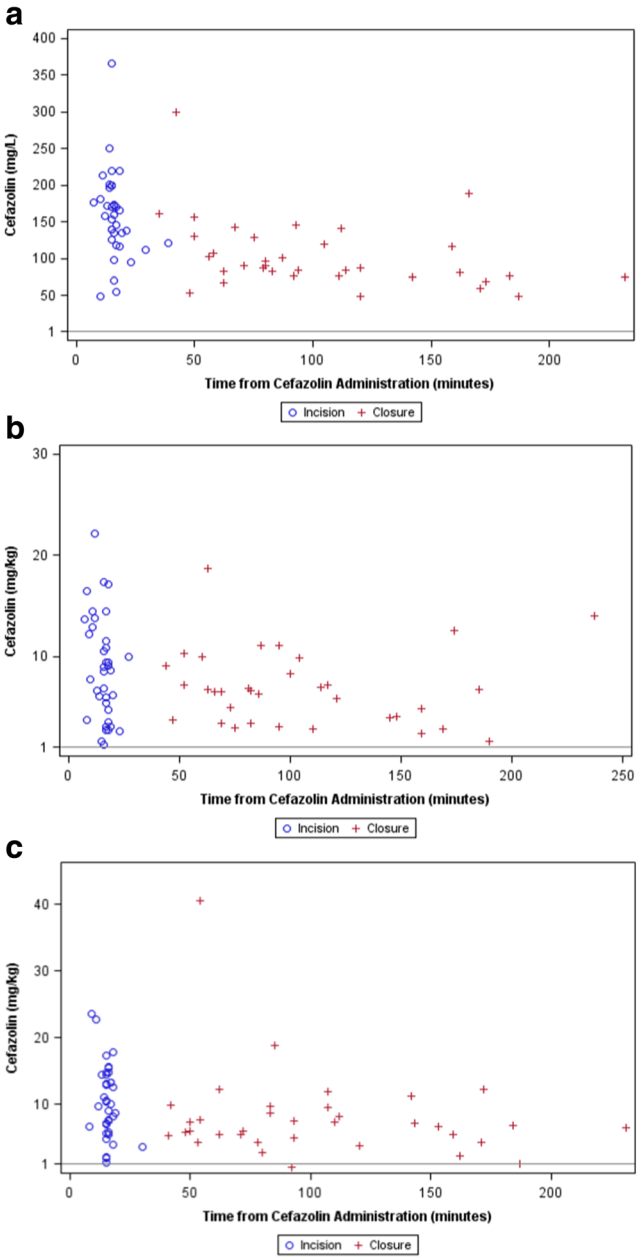

Fig. 1 Cefazolin concentration over time. **a** Cefazolin concentration in serum. **b** Cefazolin concentration in subcutaneous adipose tissue. **c** Cefazolin concentration in peri-gastric adipose tissue

Since increasing the dose of cefazolin (lipid insoluble) increases serum, but not adipose tissue levels, our findings argue against weight-based dosing in obese patients, i.e., extremely high doses (3–4 g) are no more effective than 2-g cefazolin (in bariatric surgery).

Our PK data showed that as BMI increased, cefazolin concentrations decreased. The limitations of our study were that the study group was small and did not include patients with moderate/severe renal impairment which would increase cefazolin study serum concentrations.

Our study was a PK and was not an efficacy study and demonstrated that in bariatric surgery a single preoperative prophylactic dose of cefazolin 2 g (IV bolus given over 3–5 min just before skin incision) provides optimal protective cefazolin concentrations in adipose tissue more than adequate to prevent MSSA SSIs. Moreover, our data shows that despite the poor cefazolin penetration into adipose tissue (6–8 %), the concentrations in adipose tissue after a 2-g IV bolus dose were protective and well in excess of the MIC of *S. aureus* (MSSA). Although therapeutic concentrations of cefazolin persist in adipose tissue for 4.8 h, effective prophylaxis, due to the PAE, is maintained for >4 h eliminating the need for intraoperative redosing.

Therefore, we conclude that cefazolin administered as a 2 g dose (IV bolus dose over 3–5 min given just before skin incision) provides optimal protective for the duration of bariatric surgical procedures cefazolin levels to maintain protective cefazolin levels for the duration of the procedure. Higher doses of cefazolin of 3–4 g are unnecessary for effective prophylaxis of SSIs in bariatric procedures. Since cefazolin penetration into adipose tissue depends on lipid solubility (V_d) and is not dose-dependent, to maintain protective cefazolin levels for the duration of the procedure. Furthermore, when cefazolin is given as a 2 g IV bolus (3–5 min just before skin incision), an additional intraoperative cefazolin dose is unnecessary to maintain protective cefazolin levels for the duration of the procedure.

Compliance with Ethical Standards

Conflict of Interest All authors declare no conflict of interest in publication of this manuscript.

Informed Consent For this type of study, formal consent is not required.

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