Pharmacokinetics and Tissue Penetration of Cefoxitin in Obesity: Implications for Risk of Surgical Site Infection

Octavian Toma, MD,* Patty Suntrup, CRRT,* Andrei Stefanescu, PhD,* Amy London, BS,* Matthew Mutch, MD,† and Evan Kharasch, MD, PhD*

BACKGROUND: Obesity is a significant risk factor for surgical site infections (SSIs), for poorly understood reasons. SSIs are a major cause of morbidity, prolonged hospitalization, and increased health care cost. Drug disposition in general is frequently altered in the obese. Preoperative antibiotic administration, achieving adequate tissue concentrations at the time of incision, is an essential strategy to prevent SSIs. Nonetheless, there is little information regarding antibiotic concentrations in obese surgical patients. This investigation tested the hypothesis that the prophylactic antibiotic cefoxitin may have delayed and/or diminished tissue penetration in the obese.

METHODS: Plasma and tissue concentrations of cefoxitin were determined in obese patients undergoing abdominal and pelvic surgery (body mass index 43 ± 10 kg/m², n = 14, 2 g cefoxitin) and in normal-weight patients and healthy volunteers (body mass index 20 ± 2 kg/m², n = 13, 1 g cefoxitin). Tissue concentrations were measured using a microdialysis probe in the subcutaneous layer of the abdomen, and in adipose tissue excised at the time of incision and wound closure.

RESULTS: Plasma concentrations and area under the concentration-time curve (AUC) were approximately 2.5-fold higher in the obese patients because of the 2-fold-higher dose. Dose-normalized concentrations were higher, although AUCs were not significantly different. Measured and dose-normalized subcutaneous cefoxitin concentrations and AUCs in the obese patients were significantly lower than in the normal-weight subjects. There was an inverse relationship between cefoxitin tissue penetration (AUCtissue/AUCplasma ratio) and body mass index. Tissue penetration was substantially lower in the obese patients (0.08 ± 0.07 vs. 0.37 ± 0.26, P < 0.05). Adipose tissue cefoxitin concentrations in obese patients were only 7.8 ± 7.3 and 2.7 ± 1.4 µg/g, respectively, at incision and closure, below the minimum inhibitory concentration of 8 and 16 µg/mL, respectively, for aerobic and anaerobic microorganisms.

CONCLUSION: Obese surgical patients have impaired tissue penetration of the prophylactic antibiotic cefoxitin, and inadequate tissue concentrations despite increased clinical dose (2 g). Inadequate tissue antibiotic concentrations may be a factor in the increased risk of SSIs in obese surgical patients. Additional studies are needed to define doses achieving adequate tissue concentrations. (Anesth Analg 2011;113:730–7)

Antibiotic prophylaxis before surgery is the standard of care and a keystone for the prevention of surgical site infections (SSIs).1–5 SSIs are the most common surgical complication, occur in up to 25% of abdominal operations, and are a major cause of morbidity, mortality, patient suffering, intensive care unit admissions, prolonged length of stay, hospital readmission, and increased health care cost.6–8 Prophylactic antibiotics decrease infectious morbidity and mortality, length of stay, and cost of care.

Effective antibiotic prophylaxis requires therapeutic drug concentrations in the tissue during the risk period for bacterial contamination, that is, from incision through closure. Timing is critical, because both early and late antibiotic administration increase SSI rates.2 Current United States guidelines dictate administration of prophylactic antibiotics within 60 minutes (120 minutes for vancomycin) of incision,2,3 to establish bactericidal concentrations in tissues by incision. A corollary expectation of preincision dosing is that tissue concentrations at the end of surgery will still be high enough to prevent infection.9,10 The current clinical recommendation is antibiotic administration at the induction of anesthesia, but this may not occur until seconds before incision.1,11 Indeed, timing is the most common problem in antibiotic prophylaxis for SSIs, attributable in part to intraoperative workflow and role perception problems.12 The National Surgical Infection Prevention Project found that prophylactic antibiotics were administered to only 56% of patients within 1 hour of incision.13

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Obesity (body mass index [BMI] >30 kg/m²; morbid obesity BMI ≥40 kg/m²) is epidemic. Approximately 68% of American adults are overweight (BMI ≥25 kg/m²), and more than one-third are obese.14 Fourteen percent have class II obesity (BMI 35–40 kg/m²) and 6% are morbidly obese, and there is significant geographical variation in the prevalence of obesity.14 Obesity is a known independent risk factor for SSIs, and this risk factor persists despite antibiotic prophylaxis.15,16 Obesity increases the risk of SSI after colectomy 2.5- to 5-fold.17

The mechanism of increased SSI in obesity is poorly understood. One theory is that tissue concentrations of prophylactic antibiotics in obese patients are inadequate.15 In one study, there was a significant association between intraoperative antibiotic concentrations (at surgical closure) and the effectiveness of antibiotic prophylaxis.18 In obese patients, subtherapeutic tissue antibiotic concentrations were associated with an increased rate of wound infections.19,20

Obesity in general can alter drug pharmacokinetics and disposition because of altered volume of distribution, regional blood flow, total body clearance, and plasma protein binding, and there is accumulating information in general about drug pharmacokinetics and dosing in obesity.21 Comparatively less is known, however, for antibiotics.22,23 Vancomycin and aminoglycosides are the only antibiotics that have been extensively studied.22,23 Their kinetics are altered in obesity, necessitating modified dosing. In general, studies of these drugs, and β-lactams/cephalosporins (cefotiam, cefotaxime, cefamandole, cefazolin, and ceftepime), have shown lower plasma and serum concentrations in obese patients because of increased volumes of distribution and systemic clearances.19–24

There is little information, however, regarding preoperative antibiotic prophylaxis in obesity. Some recommend that obese patients (>80 or >100 kg) receive a double dose of prophylactic antibiotic.2,5 The only surgical prophylactic antibiotics studied in the obese are cefazolin, ciprofloxacin, and cefuroxime. In the morbidly obese, blood and tissue cefazolin concentrations were half those in normal patients.19 As BMI increased, tissue cefazolin concentrations decreased. Even in obese patients (BMI 40–49, 50–59, and ≥60 kg/m²) given twice the normal cefazolin dose, therapeutic plasma concentrations were achieved in only 73%, 68%, and 52% of patients, respectively, and therapeutic tissue concentrations occurred in only 48%, 29%, and 10% of patients.20 Tissue penetration of ciprofloxacin in obese subjects, based on the area under the concentration-time curve (AUCtissue/AUCplasma ratio, was approximately half that of normal-weight subjects.25 This raises clinical questions regarding current prophylactic doses and timing relative to incision in obese patients.

Cefoxitin, a β-lactam/second-generation cephalosporin that has a Surgical Care Improvement Project recommendation for colorectal surgery prophylaxis,26 is the most frequently used prophylactic antibiotic in abdominal and pelvic surgery at Barnes-Jewish Hospital (BJH). If, similar to other antibiotics, cefoxitin disposition is altered in obesity, then the standard dose and timing may result in therapeutically inadequate concentrations and an increased risk of SSIs. Hence, the purpose of this study was to evaluate cefoxitin kinetics in obese surgical patients, and determine whether current practice achieves therapeutic tissue concentrations. Tissue concentrations were determined both by calibrated microdialysis27–29 and by direct quantification of excised tissue samples.

METHODS

Protocol
The original protocol for this investigation used a single-session, parallel group design evaluating plasma and tissue concentrations of cefoxitin in morbidly obese patients compared with normal-weight patients undergoing abdominal or pelvic surgery. Cefoxitin is the standard antibiotic at BJH for prophylaxis in these patients. Inclusion criteria were BMI ≥25 kg/m² (normals) or ≥30 kg/m² (obese), and elective abdominal or pelvic surgery. Exclusion criteria were allergy to cefoxitin, or renal or hepatic insufficiency. The research protocol was approved by the Washington University IRB, and all subjects provided written informed consent. Patients underwent their surgical procedure and received a general anesthetic not otherwise altered by inclusion in the protocol.

On the morning of surgery, a microdialysis probe (model 60 microdialysis catheter; CMA Microdialysis, Inc., North Chelmsford, MA) was inserted into the subcutaneous layer of the abdomen, in approximately the midaxillary line, after local infiltration of lidocaine. An additional IV catheter for blood sampling was placed in the arm contralateral to that used for drug administration. The microdialysis catheter was perfused continuously at a flow rate of 2 μL/min (T1 perfusion fluid; CMA Microdialysis, Inc.) using a model 107 microdialysis pump (CMA Microdialysis, Inc.), and samples were collected in 15-minute intervals. The probe was perfused for approximately 30 minutes, then calibrated using the retrodialysis technique,27,28 by perfusing for 30 minutes with T1 perfusion fluid containing cefoxitin (20 μg/mL, prepared fresh daily by the Investigational Drug Service at BJH). The perfusion fluid was then changed back to T1 solution for at least 30 minutes to wash out tissue cefoxitin. The sample obtained at the end of the 30-minute retrodialysis period was used to calculate probespecific recovery of cefoxitin.

Per institutional standard, cefoxitin (1 g for patients <80 kg or 2 g for those ≥80 kg, administered as a bolus over 1 minute) was administered after the induction of general anesthesia. Venous blood samples were obtained before and 2, 5, 10, 15, 20, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours after the end of cefoxitin administration. Additional blood samples were obtained at incision and at the conclusion of wound closure. Samples were centrifuged and plasma was stored for later analysis. A small (1- to 2-g) sample of subcutaneous abdominal fat was also obtained from the surgical site at the time of incision and closure. Plasma, microdialysis, and fat samples were stored at −20°C until analyzed.

Because of the demographics of our tertiary care hospital’s patient population and an unexpected dearth of normal-weight patients undergoing abdominal or pelvic surgery, the protocol was modified. Only 2 normal-weight patients were identified and enrolled by the time the obese cohort was filled (1 year), and it was projected that several
additional years would have been required to fill the normal-weight surgical cohort. Therefore 11 healthy volunteers (≤80 kg) were enrolled to augment the normal-weight cohort. These subjects underwent cefoxitin administration, blood sampling, and microdialysis as described above, but no tissue samples were obtained. The final evaluable cohorts consisted of obese subjects (14 patients; all receiving 2 g cefoxitin) and normal-weight subjects (2 patients, and 11 healthy volunteers, all receiving 1 g cefoxitin). Patient demographics are provided in Table 1.

Sample Analysis
Cefoxitin concentrations in plasma, microdialysis fluid, and subcutaneous fat were all determined by high-performance liquid chromatography tandem mass spectrometry, using a Shimadzu Prominence LC-20 dual-pump high-performance liquid chromatography system (Shimadzu Scientific Instruments, Columbia, MD) and reverse-phase column (C18 Symmetry, 30 × 2.1 mm; Waters Corporation, Milford, MA) interfaced to an API 3200 QTRAP mass spectrometer with Turbo V ion source operating in the negative electrospray mode (AB SCIEX, Foster City, CA). The mobile phase gradient was 0.1% aqueous formic acid in 22% to 100% methanol over 2 minutes, followed by reequilibration to 5% and then 22% methanol, at a flow rate of 0.5 mL/min. The mass spectrometer source temperature was 550°C, ion spray voltage was −4300, collision energy was −10 V, and the declustering potential was −30 V for cefoxitin and −10 V for the internal standard cefuroxime. Analytes were detected using multiple reaction monitoring using the following transitions: cefoxitin (m/z 426.2 to 155.8) and cefuroxime (m/z 423.0 to 207.0).

Plasma sample preparation was accomplished by mixing 25 μL plasma with 100 μL acetonitrile (containing the internal standard cefuroxime, 400 ng/mL) to precipitate plasma proteins, benchtop centrifugation for 10 minutes, mixing 50 μL of the supernatant with 200 μL water, then injecting 10 μL of the mixture for analysis. Tissue samples were prepared by mixing approximately 90 to 110 mg fat with 400 μL of 10% acetonitrile, homogenized with a handheld ultrasonic homogenizer (Sonifier; Branson Ultrasonics Corp., Danbury, CT) at setting 3 at 6 to 8 W power for 30 seconds. Approximately 50 μL homogenate aliquots were mixed with 200 μL acetonitrile containing 1 μg/mL cefuroxime internal standard. The mixture was vortexed for 10 minutes, then centrifuged for 10 minutes, then 100 μL supernatant was mixed with 100 μL water, then 10 μL of the mixture was injected for analysis. Microdialysis samples were analyzed directly, by mixing 5 μL microdialysis fluid with 100 μL of 10% methanol, and injecting 10 μL for analysis. Appropriate plasma, tissue, and microdialysis standard curves were prepared from calibration samples and used to quantify cefoxitin in patient samples using peak areas or peak area ratios. Microdialysis fluid concentrations were corrected for probe-specific recovery.

Data Analysis
Data were analyzed using noncompartmental methods, based on the AUC. For plasma, systemic clearance of cefoxitin was CL = Dose/AUC, λ was the terminal elimination rate constant, Cmax was the maximum concentration, and Tmax was the time to maximum concentration, volume of distribution based on the terminal phase was (Vz) = Dose/(AUC × λ), and steady-state volume of distribution was (Vss) = CL × mean residence time. Microdialysis fluid AUCs were similarly determined. Tissue penetration was calculated as AUCtissue/AUCplasma. Lean body weight (LBW) was calculated from total body weight (TBW) using the formula of Janmahasatian et al.21,30,31

Results are expressed as the mean ± SD. Unpaired t tests were used to assess the significance of differences between groups. The primary outcome measures were plasma and tissue cefoxitin concentrations at the time of incision. Secondary outcome measures were peak and time to peak plasma and tissue cefoxitin concentrations, cefoxitin concentrations at closure, cefoxitin pharmacokinetic parameters (clearance, volume of distribution, half-life, and tissue penetration), and the number of patients with tissue and plasma cefoxitin concentrations exceeding the minimum inhibitory concentration (MIC50) for the common pathogens. Sample size was based on the primary outcome measure, and analysis using unpaired t tests. Using published population standard deviations for cefoxitin (25%) to detect a 50% difference in concentration, 6 or 7 subjects in each group were needed to achieve 80% or 90% power, respectively. More subjects were enrolled in case of protocol failures.

RESULTS
Subject demographics are provided in Table 1. BMI of the obese patients was more than twice that of the normal-weight subjects. The normal-weight healthy volunteers were younger than the normal-weight patients and the obese patients. Plasma samples were analyzed from all subjects. Fat samples were obtained for 13 of the 14 obese patients. Because of technical difficulties, microdialysis data were obtained for 10 obese patients and 10 normal-weight subjects.

The time course of plasma cefoxitin concentrations is shown in Figure 1A, and dose-adjusted plasma drug concentration (measured concentration/dose) are shown in Figure 1B. Pharmacokinetics parameters are provided in Table 2. Plasma concentrations and pharmacokinetics parameters were similar in the normal-weight healthy volunteers and all normal-weight subjects (patients and volunteers). Plasma
subjects. Clearance was significantly less when normalized significantly different in the obese patients and normal-weight in the obese patients because of the 2-fold-higher dose, concentrations and AUCs were approximately 2-fold higher mean received 2 g, and normal-weight subjects received 1 g IV cefoxitin bolus. Results are mean ± SD.

Figure 1. Plasma cefoxitin concentrations in obese patients, normal-weight healthy volunteers, and all normal-weight subjects. Results are shown for (A) measured and (B) dose-adjusted plasma concentrations. Obese patients received 2 g, and normal-weight subjects received 1 g IV cefoxitin bolus. Results are shown for (A) measured and (B) dose-normalized concentrations. Obese subjects received 2 g cefoxitin, and normal-weight subjects received 1 g. * P < 0.05 compared with all normal-weight subjects.

Table 2. Cefoxitin Plasma Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Patients</th>
<th>Obese* (n = 14)</th>
<th>Healthy volunteers (n = 11)</th>
<th>All subjects (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>258 ± 75</td>
<td>242 ± 174</td>
<td>240 ± 170</td>
</tr>
<tr>
<td>Cmax/D (µg/mL/g)</td>
<td>129 ± 37*</td>
<td>242 ± 174</td>
<td>240 ± 170</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>3 ± 1</td>
<td>2 ± 1</td>
<td>3 ± 1</td>
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<td>AUCplasma (h · µg/mL)</td>
<td>178 ± 40*</td>
<td>71 ± 20</td>
<td>81 ± 33</td>
</tr>
<tr>
<td>AUCplasma/D (h · µg/mL/g)</td>
<td>89 ± 20</td>
<td>71 ± 20</td>
<td>81 ± 33</td>
</tr>
<tr>
<td>CL (mL/min)</td>
<td>197 ± 43</td>
<td>260 ± 90</td>
<td>240 ± 101</td>
</tr>
<tr>
<td>CL/TBW (mL/min/kg)</td>
<td>1.6 ± 0.5*</td>
<td>4.1 ± 1.0</td>
<td>3.9 ± 1.1</td>
</tr>
<tr>
<td>CL/LBW (mL/min/kg)</td>
<td>3.3 ± 1.0*</td>
<td>5.5 ± 1.3</td>
<td>5.2 ± 1.4</td>
</tr>
<tr>
<td>Vz(L)</td>
<td>19 ± 6</td>
<td>19 ± 6</td>
<td>18 ± 7</td>
</tr>
<tr>
<td>Vz/TBW (L/kg)</td>
<td>0.16 ± 0.05*</td>
<td>0.31 ± 0.08</td>
<td>0.30 ± 0.08</td>
</tr>
<tr>
<td>Vz/LBW (L/kg)</td>
<td>0.32 ± 0.10</td>
<td>0.41 ± 0.11</td>
<td>0.40 ± 0.11</td>
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<tr>
<td>Vss (L)</td>
<td>18 ± 5*</td>
<td>12 ± 4</td>
<td>11 ± 5</td>
</tr>
<tr>
<td>Vss/TBW (L/kg)</td>
<td>0.14 ± 0.04*</td>
<td>0.19 ± 0.07</td>
<td>0.19 ± 0.06</td>
</tr>
<tr>
<td>Vss/LBW (L/kg)</td>
<td>0.29 ± 0.08</td>
<td>0.25 ± 0.09</td>
<td>0.26 ± 0.09</td>
</tr>
<tr>
<td>t1/2(h)</td>
<td>1.2 ± 0.4*</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.2</td>
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</tbody>
</table>

Values are mean ± SD.

Cmax = maximum concentration; Cmax/D = dose-normalized maximum concentration; Tmax = time of maximum concentration (from end of 1-minute bolus); AUCplasma = area under plasma concentration-time curve extrapolated to infinity; AUCplasma/D = dose-normalized area under plasma concentration-time curve extrapolated to infinity; CL = clearance; CL/TBW = clearance normalized to total body weight; CL/LBW = clearance normalized to lean body weight; Vz = apparent volume of distribution based on the terminal phase; Vz/TBW = apparent volume of distribution based on the terminal phase normalized to total body weight; Vz/LBW = apparent volume of distribution based on the terminal phase normalized to lean body weight; Vss = apparent steady-state volume of distribution; Vss/TBW = apparent steady-state volume of distribution normalized to total body weight; Vss/LBW = apparent steady-state volume of distribution normalized to lean body weight; t1/2 = half-life.

Obese subjects received 2 g cefoxitin, and normal-weight subjects received 1 g. * P < 0.05 compared with all normal-weight subjects.

concentrations and AUCs were approximately 2-fold higher in the obese patients because of the 2-fold-higher dose, although there was no significant difference in Cmax. This concentration difference appeared to persist, however, after dose normalization (Fig. 1B), although the dose-normalized AUCs were not significantly different. Absolute cefoxitin clearances and volumes of distribution were not significantly different in the obese patients and normal-weight subjects. Clearance was significantly less when normalized to either TBW or LBW. Volumes of distribution were lower in obese patients when normalized to TBW, but not to LBW. There was a significant correlation between LBW and volume of distribution (r = 0.41 for Vz, r = 0.60 for Vss, P < 0.05; not shown) but not clearance. Elimination half-life was somewhat prolonged in the obese patients. There were no significant differences in pharmacokinetic parameters between the obese (BMI >30 kg/m2; mean 36 ± 3 kg/m2, n = 6) and morbidly obese (BMI ≥40 kg/m2; mean 40 ± 10 kg/m2, n = 8) patients.

The time course of subcutaneous tissue cefoxitin concentrations determined by microdialysis is shown in Figure 2A, and pharmacokinetic parameters are provided in Table 3. Dose-adjusted tissue drug concentrations are shown in Figure 2B. Subcutaneous tissue concentrations were similar in the normal-weight healthy volunteers and all normal-weight subjects. Measured subcutaneous cefoxitin concentrations in the obese patients receiving 2 g cefoxitin were generally lower than those in the normal-weight subjects receiving 1 g, and peak concentrations were approximately half those in the normal-weight subjects. Nevertheless, there was considerable interindividual variability, and the AUC and Cmax differences were not statistically significant between obese and normal-weight subjects. In contrast, the dose-normalized tissue AUC and the dose-normalized Cmax were significantly lower in the obese patients. Dose-normalized Cmax in the obese patients was less than one-third that in the normal-weight subjects. Moreover, the AUCtissue/AUCplasma ratio, reflecting the extent of antibiotic tissue penetration, was substantially and significantly lower in the obese patients (0.08 ± 0.07) compared with normal-weight subjects (0.37 ± 0.26). There was an inverse relationship between cefoxitin tissue penetration and BMI (Fig. 3), although differences in tissue penetration between the morbidly obese and obese patients (0.05 ± 0.04 vs 0.11 ± 0.08) did not achieve statistical significance. The rate of tissue penetration, measured by Tmax, was not different in the obese patients and normal-weight subjects.

Tissue cefoxitin concentrations were also measured directly in the surgical patients, in excised adipose tissue, at the time of incision and wound closure (Table 4). Adipose concentrations in the 13 obese patients were 7.8 ± 7.3 and
weight subjects were similar to those reported previously. Cefoxitin plasma pharmacokinetic parameters in normal-

DISCUSSION

Cefoxitin plasma pharmacokinetic parameters in normal-weight subjects were similar to those reported previously.  

In obese surgical patients, the systemic disposition of cefoxitin was altered. Independent of dose, Cmax was lower, clearance was decreased, and the half-life was prolonged, whereas the AUC and LBW-normalized volumes of distribution were unchanged. Volume of distribution is a major determinant of plasma concentrations. In general, Vss is a more appropriate descriptor of volume of distribution than Vss, particularly for a bolus dose. The significantly lower Vss/TBW in obese patients suggests that the hydrophilic cefoxitin does not distribute completely into the excess body weight (primarily adipose) over ideal body weight, a finding supported by the linear correlation between Vss and LBW. In addition, doubling the cefoxitin dose in the obese patients resulted in plasma concentrations exceeding those of normal-weight subjects, Cmax that was equal to that of normal-weight subjects, and an AUC twice that of normal-weight subjects. Together, these results suggest that cefoxitin dosing to achieve similar plasma concentrations should be based on LBW. A similar conclusion was reached regarding cefotaxime dosing in obesity. The major finding of this investigation was that tissue penetration of cefoxitin was markedly reduced in obese surgical patients. Despite higher plasma cefoxitin concentrations, subcutaneous and adipose tissue antibiotic concentrations were significantly lower in obesity. The overall extent of tissue cefoxitin penetration in obese surgical patients, measured as AUCtissue/AUCplasma, was reduced to only 22% of that in normal-weight subjects. There was an inverse relationship between cefoxitin tissue penetration and BMI, and tissue penetration seemed even lower in morbidly obese compared with obese patients; however, the number of patients was small and differences did not achieve statistical significance. Additional studies are needed.

| Table 3. Cefoxitin Subcutaneous Microdialysis Pharmacokinetic Parameters |
|-----------------------------------|-----------------|-----------------|-----------------|
| **Obese Patients (n = 10)**       | **Healthy volunteers (n = 8)** | **All subjects (n = 10)** |
| Cmax (µg/mL)                      | 11 ± 11         | 20 ± 14         | 22 ± 18         |
| Cmax/D (µg/mL/g)                  | 5.6 ± 5.7*      | 20 ± 14         | 22 ± 18         |
| Tmax (min)                        | 26 ± 7          | 30 ± 11         | 29 ± 11         |
| AUCtissue (h · µg/mL)             | 16 ± 13         | 23 ± 15         | 26 ± 20         |
| AUCtissue/D (h · µg/mL/g)         | 8.0 ± 6.6*      | 23 ± 15         | 26 ± 20         |
| t1/2 (h)                          | 1.2 ± 0.4*      | 0.9 ± 0.1       | 0.9 ± 0.1       |
| AUCtissue/AUCplasma               | 0.08 ± 0.07*    | 0.38 ± 0.25     | 0.37 ± 0.26     |

Values are mean ± SD.

Cmax = maximum concentration; Cmax/D = dose-normalized maximum concentration; Tmax = time of maximum concentration (from end of 1-minute bolus); AUCtissue = area under tissue concentration-time curve extrapolated to infinity; AUCtissue/D = dose-normalized area under plasma concentration-time curve extrapolated to infinity; t1/2 = half-life; AUCtissue/AUCplasma = ratio of areas under plasma and tissue concentration-time curves.

Obese subjects received 2 g cefoxitin, and normal-weight subjects received 1 g.

* P < 0.05 compared with all normal-weight subjects.

<table>
<thead>
<tr>
<th>Table 4. Cefoxitin Concentrations in Adipose Tissue at Incision and Wound Closure in Obese Surgical Patients</th>
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<tbody>
<tr>
<td><strong>Plasma (n = 14)</strong></td>
</tr>
<tr>
<td><strong>Time (h)</strong></td>
</tr>
<tr>
<td>Incision</td>
</tr>
<tr>
<td>Closure</td>
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</table>

| **Tissue (n = 13)**                                             |
| **Time (h)** | **Concentration (µg/g)** |
| Incision      | 0.35 ± 0.23 | 7.8 ± 7.3      |
| Closure       | 2.4 ± 1.4   | 2.7 ± 1.4      |

Values are mean ± SD.

a Time is relative to the dosing of cefoxitin.
needed to further assess the penetration of cefoxitin in morbidly obese patients.

Most antibiotics are hydrophilic, and significantly diminished tissue blood flow in morbid obesity can reduce and/or delay penetration of some drugs into tissue. Subcutaneous adipose tissue blood flow (milliliters per gram of fat) is 30% to 50% lower in morbidly obese compared with moderately obese or normal-weight persons. Diminished cefoxitin tissue penetration in obesity is consistent with reduced adipose tissue perfusion. Previous investigations also showed that tissue concentrations of cephalexin in obese patients were lower in morbidly obese patients, and below therapeutic concentrations. Nevertheless, based on the above considerations, the conclusion would be that 2 g cefoxitin in obese surgical patients has been abundantly cataloged, the mechanism remains unknown. Explanations offered include mechanical difficulties, diabetes, and insufficient wound tissue oxygen tension. Nevertheless, periopeative supplemental oxygen did not significantly reduce SSIs, at least in colorectal surgery. Another explanation offered is that tissue concentrations of prophylactic antibiotics may be inadequate. For example, there was a significant association between intraoperative antibiotic concentrations (at surgical closure) and the risk of postoperative wound infection and the effectiveness of antibiotic prophylaxis. In obese patients, subtherapeutic tissue cefazolin concentrations were associated with an increased rate of wound infections.

There are potential limitations to this investigation. Because of the demographics of our tertiary care hospital, and near absence of normal-weight abdominal surgery patients, a normal-weight surgical cohort was unavailable as the comparator group. The obese patients were significantly older and underwent anesthesia and surgery, whereas most of the normal-weight subjects did not, which may have potentially confounded the results. Nonetheless, there is no evidence that adipose tissue blood flow declines with age, and general anesthesia actually increases local blood flow. Hence, these do not seem to be significant confounders. Moreover, independent of the between-group comparison, the obese patients had subtherapeutic tissue antibiotic concentrations. Other potential influences on adipose tissue blood flow, such as diabetes or peripheral vascular disease, were not evaluated. Also not evaluated was cefoxitin plasma protein binding, and hence free (unbound) drug concentrations. Hence, there was not a direct comparison of unbound tissue to unbound plasma cefoxitin concentrations.

These results suggest that cefoxitin doses higher than 2 g may be needed to achieve adequate tissue antimicrobial concentrations in morbidly obese patients. Additional investigation is needed to assess the appropriate doses needed to achieve these concentrations, their effectiveness in preventing SSIs (and in comparison to the current 2-g standard), and their safety.

In summary, morbidly obese surgical patients had significantly lower and subtherapeutic tissue cefoxitin concentrations, and reduced tissue cefoxitin penetration, compared with normal-weight subjects. These occurred despite 2-fold-higher cefoxitin doses. Diminished tissue antibiotic concentrations in morbid obesity may influence the incidence of SSIs.
DISCLOSURES

Name: Octavian Toma, MD.
Contribution: Study design, study conduct, manuscript preparation.
Name: Patty Suntrup, CRRT.
Contribution: Study conduct.
Name: Andrei Stefanescu, PhD.
Contribution: Study conduct, data analysis, manuscript preparation.
Name: Amy London, BS.
Contribution: Study conduct, data analysis.
Name: Matthew Mutch, MD.
Contribution: Study design, manuscript preparation.
Name: Evan Kharasch, MD.
Contribution: Study design, study conduct, data analysis, manuscript preparation.

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Evan Kharasch statement on FAER funding: In 1990, I received an FAER award entitled “Human Alfentanil Metabolism and Inhibition by Dexametomidine.” The project aimed to understand factors that might influence the metabolism, and hence the pharmacokinetics and clinical effects of alfentanil. This FAER funding and project were important to my career development in several ways. It enabled me to learn mass spectrometry, an analytical technique that has been core to the majority of the research throughout my career. The project generated results that were used as preliminary data for extramural federal research grants that were successfully funded. The project was also the beginning of a career-long venture to understand the role of hepatic and extrahepatic drug metabolism and drug transport in the pharmacokinetics, pharmacodynamics, pharmacogenetics, toxicity, and variability in patient response, to anesthetic and nonanesthetic drugs, which are directed toward optimizing drug disposition, clinical effectiveness, and patient safety.

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