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Pharmacokinetics of cefazolin prophylaxis in obese gravidae at time of cesarean delivery

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Abstract

OBJECTIVE—To compare the pharmacokinetics of 2g and 3g doses of cefazolin when used for peri-operative prophylaxis in obese gravidae undergoing cesarean delivery.

STUDY DESIGN—We performed a double-blinded randomized controlled trial from August 2013 to April 2014. Twenty-six obese women were randomized to receive either 2g or 3g IV cefazolin within 30min of skin incision. Serial maternal plasma samples were obtained at specific time points up to 8hrs after drug administration. Umbilical cord blood was obtained after placental delivery. Maternal adipose samples were obtained prior to fascial entry, after closure of the hysterotomy and subsequent to fascial closure. Pharmacokinetic parameters were determined via non-compartmental analysis.

RESULTS—The median area under the plasma concentration vs. time curve was significantly greater in the 3g group than in the 2g group (27204 µg/mL/min vs. 14058 µg/mL/min: p=0.001).

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Maternal plasma concentrations were impacted by body mass index. For every 1 kg/m² increase in body mass index at time of cesarean delivery, there was an associated 13.77µg/mL lower plasma concentration of cefazolin across all time points (p=0.01). By the completion of cesarean delivery, cefazolin concentrations in maternal adipose were consistently above the minimal inhibitory concentration for both gram-positive and gram-negative bacteria with both the 2g and 3g doses. The median umbilical cord blood concentrations were significantly higher in the 3g vs. the 2g group (34.5 µg/mL and 21.4 µg/mL: p=.003).

CONCLUSION—Cefazolin concentrations in maternal adipose both at time of hysterotomy closure and fascial closure were above the minimal inhibitory concentration for both gram-positive and gram-negative bacteria when either 2g or 3g cefazolin was administered as perioperative surgical prophylaxis. Maternal cefazolin concentrations in plasma and maternal adipose tissue are related to both dose and body mass index.

Keywords

Cefazolin; Obesity; Cesarean Delivery; surgical prophylaxis; pharmacokinetics

INTRODUCTION

Currently, over 50% of American pregnancies are complicated by maternal overweight status or obesity.^{1–2} Obesity has been correlated with numerous adverse pregnancy outcomes such as hypertensive disorders of pregnancy, gestational diabetes, and increased rates of operative delivery.² Moreover, obesity, irrespective of pregnancy, has been demonstrated to be an independent risk factor for the development of postoperative surgical site infections (SSIs).² Development of such infections can have both long-term medical sequelae for patients and economic impacts on the health care system.

The American Congress of Obstetricians and Gynecologists (ACOG) recommends surgical prophylaxis with an appropriate antibiotic regimen within 60min of skin incision to reduce post-operative wound complications.^{3–4} The goal of antibiotic prophylaxis is to prevent skin flora from contaminating the operative field. Common skin organisms include Gram-positive bacteria (*Staphylococcus aureus*, *Streptococcus* species and enterococci), Gram-negative bacteria (*Escherichia coli*, *Proteus*, *Serratia*) and anaerobes.^{3,5} Currently accepted standards for pre-cesarean antibiotic use involves administration of 1 g of cefazolin, a first generation hydrophilic cephalosporin, to patients with a body mass index (BMI) of less than 30kg/m² and, based on bariatric literature, 2g of cefazolin for those with a BMI greater than or equal to 30kg/m².^{2, 5–6}

To be effective surgical prophylaxis, cefazolin concentrations should exceed the minimal inhibitory concentration (MIC) for gram-positive cocci (GPCs) of 1µg/g and gram-negative rods (GNRs) of 4µg/g.⁶ Few studies have examined the pharmacokinetics of cefazolin in pregnant women. Moreover, it is unclear if current antibiotic recommendations are sufficient to prevent SSIs at the time of cesarean delivery in the obese gravida. Pevzner and colleagues have suggested that antibiotic concentrations in the adipose tissue of obese women given 2g of cefazolin at the time of cesarean delivery did not reach the MIC of cefazolin for gram negative rods (GNRs), thus making this dose ineffective surgical prophylaxis.^{6–7} By

assessing the pharmacokinetic parameters of 2g versus 3g of cefazolin administered as perioperative prophylaxis in the obese gravida at the time of cesarean delivery, we aim to determine the impact of BMI and cefazolin dose on cefazolin concentrations in maternal plasma, umbilical cord blood and maternal adipose tissue.

MATERIALS and METHODS

A. Participants

We conducted a double-blinded randomized controlled trial at Magee-Womens Hospital of UPMC (Pittsburgh, Pennsylvania, USA) from August 2013 to April 2014. Eligible participants were pregnant women aged 18 years or greater with a pre-pregnancy body mass index (BMI) of 30kg/m² or more who were to be delivered via scheduled cesarean delivery. Potential participants were screened for eligibility via assessment of either the available paper medical record or electronic medical chart. Potential participants were consented at a prenatal appointment, during an encounter while in the obstetrical triage unit or in the pre-operative area on the day of presentation for their scheduled cesarean delivery. At the time of surgery, all participants had intact membranes.

Exclusion criteria included type 1 and type 2 insulin dependent diabetes mellitus, autoimmune disease including systemic lupus erythematosus or discoid lupus, chronic renal disease, chronic corticosteroid use, history of a previous wound breakdown from a cesarean delivery or any other abdominal surgical procedure, allergy to cephalosporins (e.g. anaphylaxis, urticaria or any other systemic consequences) or receipt of antibiotics within two weeks of delivery.

B. Interventions

Subsequent to enrollment, women were randomized to receive either 2g or 3g cefazolin, which was ordered from the Magee Central Pharmacy, as their pre-operative antibiotic prophylaxis. Randomization was performed by the pharmacy using www.randomizer.org, using 1:1 simple randomization. All investigators and participants were blinded to the dose assignment. This study was conducted with approval of the University of Pittsburgh Institutional Review Board.

Pre-operatively, all women had an initial 18 gauge intravenous line (IV) placed for fluid administration and intra-operative resuscitation. Following consent to randomization, women received a second 18 gauge IV placed in the opposite arm to obtain necessary maternal blood samples. A 5cc sample of maternal blood was obtained with placement of this IV line as a baseline maternal blood sample. Ringer's lactate was infused through the secondary IV line at a rate of 30cc/hr in order to maintain venous patency. Women were taken to the operating room where neuraxial anesthesia was administered. After proper anesthesia administration, cefazolin was infused rapidly over 3min via the initial IV line. The primary surgeon performed an abdominal preparation with 4% chlorhexidine gluconate solution per hospital protocol with subsequent sterile draping of the operative field. All patients received Ringer's lactate through their standard IV line for surgical resuscitation.

C. Pharmaceutical Preparation

Once a patient agreed to enrollment, a research pharmacist dispensed a 150 cc bag of 0.9% normal saline containing either 2 g or 3 g of cefazolin according to a computer generated randomization list. Bags containing either cefazolin dosage were identically labeled with the term “Cefazolin Study”, along with their respective date of pharmaceutical preparation, so as to ensure allocation concealment. Thus, all operating room personnel were blinded to the administered dose. The principal investigator was un-blinded to subject allocation only after recruitment was completed.

D. Sample collection

i. Maternal Blood—A baseline blood sample was obtained from each patient prior to cefazolin infusion. After a 3-min infusion of either dosage of cefazolin was completed, a 5cc blood sample was obtained from the secondary IV site (“time zero”). This blood sample and all further samples were obtained by discontinuing the infusion of Ringer’s lactate, drawing off 5mL of fluid before obtaining the actual blood sample for analysis. Samples were collected in a 6mL pink top K2 EDTA vacutainer blood collection tube. The secondary IV line was then flushed and the Ringer’s lactate infusion re-started. Subsequent maternal blood samples were similarly obtained at the following times after completion of the infusion: 15min, 30min, 60min, 2hrs, 4hrs, 6hrs and 8hrs. After the last sample, the secondary IV site was discontinued. All blood samples were centrifuged at 4000g for 5min within 10min of obtaining the sample, or placed on ice for later centrifugation if it could not occur within that time span. Three-1mL aliquots of the supernatant plasma from each sample were placed into 2mL microfuge tubes and stored at -80°C for future analysis.

ii. Umbilical Cord Blood—After delivery of the fetus, the primary surgeon provided investigators with an isolated segment of umbilical cord from the remaining placenta. A 5mL sample of blood was obtained from the umbilical vein and subsequently centrifuged at 4000g for 5min. Three-1mL aliquots of the supernatant from each sample were placed into 2 mL microfuge tubes and stored at -80°C until future analysis. No direct venipuncture of any neonate was performed.

iii. Maternal Adipose Tissue—Quarter-sized (25 mm) samples of maternal subcutaneous adipose tissue were obtained at three separate time points during surgery: prior to rectus fascial entry, after hysterotomy closure and after fascial closure. Samples were removed via use of Mayo scissors or electrocautery. Once obtained, adipose samples were placed into individually labeled sterile sampling bags. Once sealed, all bags were immediately flash frozen in liquid nitrogen and then stored at -80°C for future analysis.

iv. Maternal Urine—Cumulative maternal urine was obtained after 2hrs, 4hrs and 8hrs post cefazolin administration to aid in calculation of maternal cefazolin clearance. Total urine produced was collected and recorded at each interval, with 30cc being aliquoted into two separate 15cc conical tubes. Samples were sealed in biohazard bags and stored at -80°C for future analysis.

E. Sample Processing, Preparation and Analysis

Cefazolin concentrations in maternal plasma and umbilical cord blood samples were analyzed using a validated liquid chromatography-mass spectrometry (LC-MS) method.^{8–9} Maternal adipose tissue samples were homogenized in a 3:1 ratio of deionized water to adipose tissue and subsequently analyzed in accordance with a previously established method by Dudley et al.¹⁰

F. Statistical Analysis

Use of 2g cefazolin in women with a BMI greater than 40kg/m² versus those with a BMI less than 30kg/m² by Pevzner et al revealed an almost 50% difference in cefazolin adipose concentrations at the end of cesarean delivery (4.35µg/g vs. 9.37 µg/g, p<0.001).⁷ In using a 2g vs. 3g two-tailed strategy, and assuming a 50% increase in tissue concentrations in the 3g group over the 2g group, with an alpha error 0.05 and power of 80%, approximately 26 total patients would be needed for this study. Non-compartmental analysis was performed in order to determine the following pharmacokinetic parameters: area under the plasma concentration versus time (AUC) curve, volume of distribution (Vd), plasma clearance (Clp) and half-life (T_{1/2}). All data were assumed to be non-normally distributed. The Wilcoxon sign-rank test was used to assess the medians of point-wise comparisons between the two randomized groups. Generalized linear models (GLM) assessed for differences between groups across the entire period in which plasma samples were obtained while simultaneously controlling for correlation of repeated measures within subjects, accounting for interactions of BMI and dose over a period of time. Differences in cefazolin concentrations in adipose tissue were analyzed via the Wilcoxon rank-sum test under the assumption of a non-parametric distribution of concentrations. Statistical analysis was performed using STATA 13.0 (College Station, TX). P-values less than 0.05 were considered statistically significant.

RESULTS

Figure 1 describes the randomization scheme. A total of twenty-eight total women were recruited into the study between August 2013 and April 2014 with twenty-six available for analysis. Demographics of the study participants are outlined in Table 1. The median estimated blood loss for all participants was 800 cc in both groups (2g IQR 700–800cc vs. 3g IQR: 800–800cc, P=0.54). Both the 2g and 3g groups were well matched for demographic parameters; however, women in the 3g group exhibited a statistically significant greater gestational weight gain as compared to their 2g counterparts, though BMI at the time of surgery was similar.

A. Maternal Plasma and Umbilical Cord Blood

Table 2 displays the individual pharmacokinetic parameters in the two randomized groups. Compared to the 2g group, the median area under the cefazolin plasma concentration versus time curve from time zero to 8 hours (AUC_{0→8}) in maternal plasma was significantly greater in the 3g group (14058 µg/mL/min vs. 27204 µg/mL/min, respectively: p=0.001). Maternal plasma clearances and the volumes of distribution of cefazolin were similar in both

the 2g and 3g group. Across the entirety of the sampling period of 8 hours, cefazolin concentrations were lower in the 2g group at each time point ($p<0.001$) (Figure 2).

To control for repeated measurements of maternal cefazolin plasma concentrations within patients, we used GLM as a method both to detect differences between the 2g and 3 g groups along the entirety of the dosing interval curve and to create a model of expected plasma concentrations with respect to BMI at the time of surgery, cefazolin dose and the time at which the plasma was measured. Figure 3 demonstrates the repeated measures model, which yielded the following equation:

$$Plasma [Cefazolin]_{expected} = 848.65 + 207.58 * (Dose) - 1.6987 * (Time) - 13.7696 * (SurgBMI) + 0.0272 * (Time * SurgBMI) - 0.3581 * (Time * Dose)$$

According to the model, a 1kg/m^2 increase in BMI at the time of cesarean delivery was associated with a $13.77\mu\text{g/mL}$ lower concentration of cefazolin throughout the measuring interval ($p=0.01$). Thus, if given the same dose of cefazolin as surgical prophylaxis, an obese woman with a higher BMI at the time of cesarean delivery would have lower plasma concentrations relative to an obese woman with a lower surgical BMI. Furthermore, in considering the interaction of time and antibiotic dose in our model, such a relationship is maintained throughout the entirety of the measuring interval of 8 hours.

Umbilical cefazolin concentrations were consistently higher in the 3 g group as compared to the 2 g group. Median cefazolin concentrations were $34.5\mu\text{g/mL}$ and $21.4\mu\text{g/mL}$ in the 3 g and the 2 g groups, respectively ($p=0.003$). Increasing from 2g to 3g results in significantly higher umbilical cord blood concentrations. Thus, this suggests rapid trans-placental transfer of cefazolin.

B. Maternal Adipose Tissue

Table 3 demonstrates the cefazolin concentrations in maternal adipose tissue obtained during cesarean delivery, as expressed by micrograms of cefazolin per gram of adipose tissue. Among the adipose samples, 92.3% of adipose samples in the 2g group were greater than or equal to $4\mu\text{g/g}$ prior to fascial entry whereas 83.3% of adipose samples in the 3g group reached such a level at the same time. Median cefazolin concentrations in adipose samples taken immediately prior to fascial entry (median time from start of infusion: 3–4min) were not statistically different between the 2g and 3g groups ($7.4\mu\text{g/g}$ vs. $12.0\mu\text{g/g}$; $p=0.18$). The samples taken at time of hysterotomy closure (median time from start of infusion: 25–28min) and at fascial closure (median time from start of infusion: 41.5–51min) were consistently above $4\mu\text{g/g}$ at all other assayed time points in both groups. The median cefazolin concentrations in adipose tissue samples obtained around the time of hysterotomy closure were significantly higher in the 3g group ($12.4\mu\text{g/g}$ vs. $16.8\mu\text{g/g}$; $P=0.02$) as well as at fascial closure ($11.8\mu\text{g/g}$ vs. $14.6\mu\text{g/g}$; $P=0.04$). In evaluating adipose tissue cefazolin concentrations from the beginning to the end of the cesarean delivery, the area under the concentration vs. time curve ($AUC_{0 \rightarrow \text{fascial closure}}$) was calculated for both the 2g and 3g individuals. The median $AUC_{0 \rightarrow \text{fascial closure}}$ was significantly higher in the 3g group as compared to the 2g group ($15.02\mu\text{g*hr/g}$ vs. $7.51\mu\text{g*h/g}$; $p=0.0022$).

COMMENT

Our results demonstrate that maternal plasma cefazolin concentrations in the perioperative period are dependent on both the initial prophylactic dose and the patient's BMI at the time of surgery. Cefazolin concentrations in maternal adipose tissue appear related to the initial prophylactic cefazolin dose and the time from the initiation of the cefazolin infusion. The objective of perioperative antibiotic prophylaxis for cesarean delivery is to reduce postoperative infection presumably by delivering adequate antibiotic to the surgical site in order to suppress bacterial growth. While the incidence of post-cesarean wound infection in all-comers is 1–2%, surgical prophylaxis decreases this complication and subsequent maternal morbidity by 60%.^{3,4,11} We have demonstrated that in obese women, both a 2g and 3g dose of cefazolin achieve sufficient adipose tissue concentrations to provide prophylaxis against gram-positive and gram-negative bacteria. Compared to those receiving 2g, those receiving 3g of cefazolin had significantly higher adipose tissue concentrations at the time of closure of the hysterotomy and at fascial closure. We have also confirmed the findings of others that BMI affects maternal cefazolin plasma concentrations.⁷

While current recommendations suggest perioperative prophylaxis for cesarean deliveries to be initiated within 60min of skin incision², this recommendation does not describe a definitive point in time at which cefazolin should be provided in order to obtain adequate tissue levels for prophylaxis. We designated 4µg/g to be MIC of GNRs in adipose in conjunction with previous work; however, more recent work suggests the MIC of some GNRs to be as high as 8µg/g due to the ever-evolving nature of bacteria either partially or fully resistant to previous effective antibiotic therapy.¹² Our adipose tissue samples still demonstrated a level consistently above such a threshold even at a time with the cesarean delivery is nearly completed, with those receiving 3g having higher tissue concentrations than those among women receiving 2g, at all time points. However, levels assayed on samples prior to fascial entry for those receiving 2g would be below this threshold, which may be a function of the point at which the infusion was initiated relative to the time of initial incision. This would suggest that for certain bacteria, 3g may be the appropriate dose in obese gravidae. Modeling of tissue levels relative to plasma levels may assist in determining the optimal timing of antibiotic administration. Consideration of a local resistance pattern and antibiogram will be important as well in order to achieve acceptable surgical prophylaxis at a tissue level.

Much of the current, limited understanding of the impact of obesity on antibiotic pharmacokinetics and pharmacodynamics is derived from the general surgical literature.¹³ Ho et al administered 2g cefazolin preoperatively to morbidly obese patients undergoing elective surgery, with plasma levels being assayed at specific times up to 4hrs post administration.¹⁴ There was no difference observed in plasma concentrations between those with BMIs between 40–49kg/m² and greater than 50kg/m².¹⁴ However, surgical-site and adipose tissue concentrations were not investigated in this study. Moreover, studies in bariatric patients have included subjects who are older in comparison to obstetric patients, which may impact pharmacokinetic parameters such as drug clearance.¹⁵ Toma and colleagues demonstrated that obese surgical patients have a statistically significant decreased antibiotic concentration at the tissue level as compared to normal BMI controls;

however, cefoxitin, a cephalosporin with similar physicochemical characteristics to cefazolin, was the drug of choice for surgical prophylaxis.¹⁵ Nevertheless, obesity impacted the efficacy of antibiotic prophylaxis.

Our study is not without limitations. No women were found to develop postpartum endometritis or a postpartum wound infection. However, while we do recognize that the frequency of SSIs is the parameter by which alterations in maternal dosing should be made; our study was not powered to evaluate the effect of a dosing regimen on the occurrence of post-cesarean SSIs. In increasing the maternal dosage of antibiotics, one must be cognizant of any impact on the fetus/neonate. Our findings, with a statistically significant increase of umbilical cord blood concentrations of cefazolin in the 3 g group as compared to the 2 g group, demonstrated the rapid trans-placental transfer of the drug to the neonate. While cefazolin is considered safe for use in pregnancy, it is unclear what fetal/neonate effects, if any, there would be with an increased maternal dosage and corresponding increase in fetal exposure. Our study was not powered to detect effects of maternal dose alterations on the pharmacodynamics of cefazolin, decreases in the incidence of SSIs or any potential neonatal outcomes. It would be important to understand such data in relation to maternal dose alterations.

In conclusion, obese women administered either a 2g or 3g dose of cefazolin appear to achieve appropriate maternal adipose tissue levels above the MIC of causative organisms of SSIs. Therefore, we do not recommend alteration in currently accepted standards of practice. Moreover, maternal obesity at the time of cesarean delivery alters perioperative antibiotic concentrations in maternal plasma, thus impacting tissue drug concentrations. Further work to evaluate alterations in maternal dose on the incidence of SSIs is warranted.

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Figure 1. Flow Chart of Randomization
Randomization scheme for the 2g and 3g group.

Figure 2. Maternal Plasma Cefazolin Concentrations

Maternal plasma cefazolin concentrations were assayed at specific time points for up to 8 hours post-administration. The dotted line with solid boxes demonstrates the median concentrations at specific time points among those receiving 3 g. The solid line with triangles demonstrates the median concentrations at specific time points among those receiving 2 g.

Figure 3. Relationship between Plasma Cefazolin Concentration and Maternal Body Mass Index
Generalized linear model (GLM) of the relationship between maternal plasma cefazolin dose and maternal body mass index at the time of surgery comparing differences in body mass index and differences in maternal dose.

TABLE 1

Demographic Data of Study Participants

Variable ¹	2 Grams Dose (n=13)	3 Grams Dose (n=13)	P-value
Gestational Age at Delivery (weeks)	39.3 (39 – 39.4)	39 (38 – 39)	0.24
Maternal Age (years)	29.0 (23.5 – 34.0)	31 (30.0 – 35.0)	0.21
Race			
Caucasian	7 (53.85%)	6 (46.15%)	
African-American	5 (38.46%)	4 (30.77%)	
Hispanic/Latino	0 (0%)	3 (23.08%)	
Asian/Pacific Islander	1 (7.69%)	0 (0%)	
Pre-Pregnancy BMI (kg/m ²)	39.6 (34.37–42.2)	36.1 (32.8–40.6)	0.19
BMI at time of surgery (kg/m ²)	42.9 (39.1–46.2)	41.8 (37.3 – 44.6)	0.63
Gestational Weight Gain (kg)	7.18 (4.40–10.44)	11.27 (8.17–16.33)	0.04
Total Operative Time (min)	59.77 (50–65)	67.38 (56–72)	0.17
Intravenous Fluids administered in operating room (mL)	1600 (1300 – 2000)	1500 (1300 – 2000)	0.96
Hemoglobin value (g/dL)			
Pre-operative	12.3 (11.5 – 12.6)	11.8 (11.2 – 12.2)	0.29
Post-operative	10.9 (10.15 – 11.9)	10.4 (10.2 – 10.9)	0.29

TABLE 2**Pharmacokinetic Parameters**

Pharmacokinetic Parameter^I	2g group	3g group	P-value
Area under the plasma concentration vs. time curve (µg/mL/min)	14058 ± 1342.8	27204 ± 2365.8	0.001
Half-life of Cefazolin (min)	107.8 ± 6.26	123.3 ± 8.2	0.13
Plasma Clearance Rate (L/min)	0.14 ± 0.01	0.11 ± 0.01	0.21
Plasma Volume of Distribution (L/kg)	13.36 ± 1.11	13.45 ± 1.48	0.48
Umbilical Cord Blood Clearance Rate (µg/ml)	21.4 ± 1.49	34.5 ± 5.77	<0.001
Plasma Volume of Distribution at Steady State (L/kg)	19.8 ± 1.15	18.6 ± 1.4	0.48
Umbilical Cord Plasma Concentration to Maternal Plasma Concentration Ratio	0.18 ± 0.02	0.22 ± 0.06	0.37
Maternal Renal Clearance (mL/min)	18.8 ± 4.8	22.5 ± 2.8	0.83

^IData presented as median ± standard error of the median.

TABLE 3

Adipose Tissue Concentrations based on Maternal Perioperative Dose

Variable ^I	2g	3g	P-value
Pre-Fascial Entry			
Time (min)	4 (2 – 6)	3 (1 – 10)	0.94
Concentration (µg/g)	7.4 (5.4 – 9.4)	12.0 (5.4 – 16.0)	0.18
Closure of Hysterotomy			
Time (min)	25 (22 – 38)	28 (22 – 37)	0.34
Concentration (µg/g)	12.4 (10 – 14)	16.8 (13.0 – 23.0)	0.02
Post-Fascial Closure			
Time (min)	41.5 (35 – 54.5)	51 (37 – 63)	0.17
Concentration (µg/g)	11.8 (9.2 – 16.2)	14.6 (10.8 – 20.8)	0.04

^I Adipose tissue concentrations based on maternal perioperative dose of either 2g or 3g cefazolin. Median time (min) at which sample obtained from initiation of infusion and concentration of cefazolin per gram of adipose tissue (µg/g). Adipose samples as follows: Pre-fascial entry, immediately after hysterotomy closure, and post-fascial closure. Data expressed as median (interquartile range).