OBSTETRICS

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

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OBJECTIVE: The objective of the study was to compare the pharmacokinetics of 2 g and 3 g doses of cefazolin when used for perioperative 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 2 or 3 g intravenous cefazolin within 30 minutes of a skin incision. Serial maternal plasma samples were obtained at specific time points up to 8 hours 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 noncompartmental analysis.

RESULTS: The median area under the plasma concentration vs time curve was significantly greater in the 3 g group than in the 2 g group (27204 μg/mL per minute vs 14058 μg/mL per minute; $P = .001$). Maternal plasma concentrations had an impact by body mass index. For every 1 kg/m^2 increase in body mass index at the time of the cesarean delivery, there was an associated 13.77 μg/mL lower plasma concentration of cefazolin across all time points ($P = .01$). 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 2 g and 3 g doses. The median umbilical cord blood concentrations were significantly higher in the 3 g vs the 2 g 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 2 g or 3 g 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.

Key words: cefazolin, cesarean delivery, obesity, pharmacokinetics, surgical prophylaxis

Cite this article as: Young OM, Shaik IH, Twedt R, et al. Pharmacokinetics of cefazolin prophylaxis in obese gravidae at time of cesarean delivery. Am J Obstet Gynecol 2015;213:541.e1-7.

Currently more than 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 recommends surgical prophylaxis with an appropriate antibiotic regimen within 60 minutes of

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Received March 28, 2015; revised May 15, 2015; accepted June 15, 2015.

This study was supported by a Magee Clinical Trainee Research Award from the Magee-Womens Research Institute grant no. 8066 (O.M.Y.) and in part by the Obstetric-Fetal Pharmacology Research Unit Network (grant 5U10HD047905), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (S.N.C. and R.V.).

The authors report no conflict of interest.

The funding source had no role in study design, data collection, data analysis, data interpretation, or decision for publication.

Presented, in part, in poster format at the 35th annual meeting of the Society for Maternal-Fetal Medicine, San Diego, CA, Feb. 2-7, 2015.

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0002-9378/$36.00 • http://dx.doi.org/10.1016/j.ajog.2015.06.034

skin incision to reduce postoperative 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 precesarean delivery antibiotic use involves the administration of 1 g of cefazolin, a first-generation hydrophilic cephalosporin, to patients with a body mass index (BMI) of less than 30 kg/m^2 and, based on bariatric literature, 2 g of cefazolin for those with a BMI of 30 kg/m^2 or greater.[2,5,6]

To be an effective surgical prophylaxis, cefazolin concentrations should exceed the minimal inhibitory concentration (MIC) for Gram-positive cocci of 1 μg/g and Gram-negative rods (GNRs) of 4 μg/g.[6] Few studies have examined the pharmacokinetics of cefazolin in pregnant women. Moreover, it is unclear whether current antibiotic recommendations are sufficient to prevent SSIs at the time of cesarean delivery in the obese gravida.

Pevzner et al[7] have suggested that antibiotic concentrations in the adipose tissue of obese women given 2 g of cefazolin at the time of cesarean delivery did not reach the MIC of cefazolin for GNRs, thus making this dose ineffective surgical prophylaxis. By assessing the pharmacokinetic parameters of 2 g vs 3 g 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

Participants

We conducted a double-blinded, randomized controlled trial at Magee-Womens Hospital of University of Pittsburgh Medical Center (Pittsburgh, PA) from August 2013 to April 2014. Eligible participants were pregnant women aged 18 years or older with a prepregnancy BMI of 30 kg/m^2 or greater 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 preoperative 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 (eg, anaphylaxis, urticaria, or any other systemic consequences), or receipt of antibiotics within 2 weeks of delivery.

Interventions

Subsequent to enrollment, women were randomized to receive either 2 g or 3 g cefazolin, which was ordered from the Magee Central Pharmacy, as their preoperative antibiotic prophylaxis. Randomization was performed by the pharmacy (using www.randomizer.org), using a 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.

Preoperatively, all women had an initial 18-gauge intravenous line (IV) placed for fluid administration and intraoperative resuscitation. Following consent to randomization, women received a second 18-gauge IV line placed in the opposite arm to obtain necessary maternal blood samples. A 5 mL 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 30 mL/h to maintain venous patency.

Women were taken to the operating room in which neuraxial anesthesia was administered. After proper anesthesia administration, cefazolin was infused rapidly over 3 minutes 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.

Pharmaceutical preparation

Once a patient agreed to enrollment, a research pharmacist dispensed a 150 mL 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 to ensure allocation concealment. Thus, all operating room personnel were blinded to the administered dose. The principal investigator was unblinded to subject allocation only after recruitment was completed.

Sample collection

Maternal blood

A baseline blood sample was obtained from each patient prior to cefazolin infusion. After a 3 minute infusion of either dosage of cefazolin was completed, a 5 mL 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 5 mL of fluid before obtaining the actual blood sample for analysis. Samples were collected in a 6 mL pink top K2 EDTA vacutainer blood collection tube.

The secondary IV line was then flushed and the Ringer's lactate infusion restarted. Subsequent maternal blood samples were similarly obtained at the following times after completion of the infusion: 15 minutes, 30 minutes, 60 minutes, 2 hours, 4 hours, 6 hours, and 8 hours. After the last sample, the secondary IV site was discontinued. All blood samples were centrifuged at 4000 $\times$ *g* for 5 minutes within 10 minutes of obtaining the sample or placed on ice for later centrifugation if it could