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Comparative total and unbound pharmacokinetics of cefazolin administered by bolus *versus* continuous infusion in patients undergoing major surgery: a randomized controlled trial

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Abstract

Background. Perioperative administration of cefazolin reduces the incidence of perioperative infections. Intraoperative re-dosing of cefazolin is commonly given between 2 and 5 h after the initial dose. This study was undertaken to determine whether intraoperative continuous infusions of cefazolin achieve better probability of target attainment (PTA) and fractional target attainment (FTA) than intermittent dosing.

Methods. Patients undergoing major surgery received cefazolin 2 g before surgical incision. They were subsequently randomized to receive either an intermittent bolus (2 g every 4 h) or continuous infusion (500 mg h^{-1}) of cefazolin until skin closure. Blood samples were analysed for total and unbound cefazolin concentrations using a validated chromatographic method. Population pharmacokinetic modelling was performed using Pmetrics® software. Calculations of PTA and FTA were performed for common pathogens.

Results. Ten patients were enrolled in each arm. A two-compartment linear model best described the time course of the total plasma cefazolin concentrations. The covariates that improved the model were body weight and creatinine clearance. Protein binding varied with time [mean (range) 69 (44–80)%] with a fixed 21% unbound value of cefazolin used for the simulations (120 min post-initial dosing). Mean (SD) central volume of distribution was 5.73 (2.42) litres, and total cefazolin clearance was 4.72 (1.1) litres h^{-1}. Continuous infusions of cefazolin consistently achieved better drug exposures and FTA for different weight and creatinine clearances, particularly for less susceptible pathogens.

Conclusions. Our study demonstrates that intraoperative continuous infusions of cefazolin increase the achievement of target plasma concentrations, even with lower infusion doses. Renal function and body weight are important when considering the need for alternative dosing regimens.

Clinical trial registration. NCT02058979.

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Key words: antibiotic prophylaxis; cefazolin; pharmacokinetics

Editor's key points

- Cefazolin is a first generation cephalosporin commonly used for perioperative surgical site infection prophylaxis.
- The time that the free fraction exceeds the minimal inhibitory concentration ($fT>MIC$) determines efficacy.
- The authors studied the probability of target concentration attainment with intermittent boluses and continuous infusions.
- Intraoperative infusions increased the achievement of target plasma concentrations even with lower infusion doses.

Surgical site infections (SSIs) are a significant cause of postoperative morbidity, with rates varying between 1 and 11%.[1 2] Administration of an appropriate antibiotic, such as cefazolin, before incision significantly reduces the risk of developing an SSI.[1] After the pre-incision dose of cefazolin, which is administered up to 60 min before surgery, re-dosing intervals vary between 2 and 5 h based on a combination of drug properties and patient- and surgery-specific factors.[3]

Currently, re-dosing of perioperative cefazolin is recommended when the duration of surgery exceeds one-to-two drug half-lives or if there is excessive blood loss (>1500 ml).[4] Subtherapeutic plasma drug concentrations requiring modification of the re-dosing interval are also seen with rapid changes in the volume of distribution, such as during cardiopulmonary bypass,[5] burns, or with changes in renal function.[6]

Cefazolin is a time-dependent antibiotic that demonstrates maximal efficacy when serum concentrations are above the minimal inhibitory concentration (MIC; $fT>MIC$). Generally, *in vitro* bacteriostatic and bactericidal activities for β-lactam antibiotics, such as cefazolin, are present when free plasma concentrations are maintained above the MIC for 35–40 and 60–70% of the dosing interval, respectively.[7 8] However, in critically ill and immunocompromised patients clinical outcomes appear to be improved if the $fT>MIC$ for cephalosporins is 100% of the dosing interval.[9] For perioperative surgical prophylaxis, the goal is also to maintain free drug concentrations above $fT>MIC$ for 90–100% of the dosing interval.[10] There are currently limited studies investigating the perioperative pharmacokinetics of cefazolin and when re-dosing should occur subsequent to the pre-incision dose. Furthermore, there are few data to describe whether use of a continuous infusion of cefazolin may increase the likelihood of maintaining effective concentrations throughout the surgical procedure.

In this randomized open-label study, we compared the population pharmacokinetics and the likely success of treatment of cefazolin administered by intermittent *vs* continuous infusion during major surgery. We hypothesized that continuous infusions of cefazolin (after a standard pre-incision dose) are more effective in achieving the *a priori* probability of target attainment (PTA) of 100% $fT>MIC$ against at least 90% of bacterial isolates than an intermittent dosing regimen.

Methods

This was a prospective open-label observational randomized controlled pharmacokinetic trial. The study was approved by the University of Virginia Institutional Review Board (UVA HSR #17266) and was registered under Clinical Trial number: NCT02058979. Written consent was obtained before randomization. A CONSORT diagram is provided in the Supplementry material, Fig. S1.

Patient selection and data collection

All patients undergoing major urological or multilevel spine surgery were screened. We recruited subjects between 18 and 80 yr of age whose weight was <120 kg with an arterial line. Exclusion criteria included patients with an allergy to β-lactams, pregnant females, creatinine clearance <30 ml min^{-1}, and those patients who received cefazolin within 72 h before surgery.

Anaesthesia management

Induction and maintenance of anaesthesia, fluid management, autologous and allogeneic transfusion, and administration of intraoperative analgesia were at the discretion of the attending anaesthestist.

Study protocol

Between 15 and 60 min before surgical incision, 2 g of cefazolin (2 g cefazolin diluted in 50 ml of 5% dextrose water; final concentration 40 mg ml^{-1}) was administered i.v. during 5 min in both the intermittent bolus and continuous infusion groups, consistent with current Surgical Care Improvement Project (SCIP) guidelines.[11]

Randomization used a block design, with the stratification factor being the sex of the subject. The block sizes of both arms were five males and five females per arm. Patients were randomized to either an intermittent bolus or a continuous infusion group. The research staff performed the randomization.

In the intermittent bolus group, cefazolin 2 g was administered every 4 h until skin closure after the initial pre-incision.

In the continuous infusion group, a cefazolin infusion was started immediately after the 2 g pre-incision dose. The continuous infusion dose was prepared as described for the pre-incision dose. The infusion rate was set to deliver 500 mg h^{-1} (12.5 ml h^{-1} of the study drug) and was continued until skin closure.

The University of Virginia Research Pharmacy supplied the study drug for both the intermittent bolus and continuous infusion groups. Postoperative cefazolin administration was at the discretion of the surgical team managing the patient and was consistent with institutional and national guidelines.[3]

Sample collection, storage, and measurement

Blood samples to determine plasma cefazolin concentrations were obtained before the pre-incision dose and after administration of the pre-incision dose at 2.5, 5, 10, 15, 20, 30, 45, 60, and every 30 min until skin closure. Blood samples were obtained from an arterial line. Blood samples were immediately placed