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Subcutaneous cefazolin to reduce surgical site infections in a porcine model

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ARTICLE INFO

Article history:
Received 23 July 2017
Received in revised form
25 September 2017
Accepted 21 November 2017
Available online xxx

Keywords:
Surgical site infections
Prophylaxis
Cefazolin
Subcutaneous
Pharmacokinetics

ABSTRACT

Background: Surgical site infections (SSIs) pose a significant health and financial burden. A key aspect of appropriate prophylaxis is the administration of antibiotics intravenously (IV). However, subcutaneous administration of antibiotics is not well described in the literature. During surgery, we hypothesize that subcutaneous injection may provide better protection against SSIs. To better understand the kinetics after subcutaneous injection, we describe the serum concentrations of cefazolin in a porcine model.

Materials and methods: Juvenile mini-Yucatan pigs were administered 20 mL of 25 mg/kg cefazolin subcutaneously, and serial blood samples were taken for 3 h. Blood samples were analyzed for cefazolin concentration using chromatography. Pharmacokinetic data were calculated based on the blood serum concentrations.

Results: Maximum serum concentrations of cefazolin were achieved 42.6 ± 2.0 min after the time of injection and were found to be 18.8 ± 7.4 μg/mL. The elimination rate constant was 0.0033 ± 0.0016 min^{-1} and the half-life was 266 ± 149 min. The area under the curve was 4940 ± 1030 μg × min/mL. The relative bioavailability of subcutaneous injection was 95% +5%/−20%.

Conclusions: Subcutaneous administration of cefazolin achieves a significantly lower maximum serum concentration than IV injection. As a result, higher doses of antibiotic can be injected locally without incurring systemic toxicity. Subcutaneous administration will therefore result in higher concentrations of antibiotic for a longer time at the incision site compared with standard IV administration. This strategy of antibiotic delivery may be more effective in preventing SSIs. Further studies are needed to detail the exact effect of subcutaneous antibiotic injection on SSI rates.

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0022-4804/$ – see front matter © 2017 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.jss.2017.11.056

Introduction

Surgical site infections (SSIs) are the most common type of healthcare-associated infection.[1,2] The incidence is 2%-5% of all patients having any surgery in the United States, although as high as 30% for some procedures such as patients having colorectal surgery.[3-5] SSIs pose both a significant medical burden to patients and a significant financial burden to the health-care industry. They increase the length of stay after an operation by 7-11 days and increase mortality risk by 2-11 times. SSIs are believed to add $3.5-$10 billion annually in cost to US health-care spending.[1,6-9]

One of the mainstays of SSI prevention is intravenous (IV) antibiotic prophylaxis before incision.[5,6] In some cases, local and topical antibiotics have been used as an adjunct to IV antibiotics to help further reduce the rate of SSIs.[10,11] However, the subcutaneous administration of antibiotics to decrease SSI rate has not been well studied. This route of antibiotic administration has been used in other countries and appears to be a convenient method of drug delivery in certain cases.[12-14] During surgery, we hypothesize that subcutaneous injection may provide higher local concentrations of antibiotic at the incision site for a longer time and thus will lower the rate of SSIs. To better understand the kinetics after subcutaneous injection, we describe the serum concentration levels of cefazolin in a porcine model as an estimate of the subcutaneous concentrations.

Materials and methods

Experimental design

The use of all animals was approved by the Animal Research Committee (institutional review board no. 2014-142-02E). Inhaled gas anesthesia was administered to female juvenile mini-Yucatan pigs weighing 6.5-11.5 kg ($n = 4$). A left femoral arterial catheter was placed under direct visualization via cutdown. The pigs were administered 20 mL of 25 mg/kg cefazolin subcutaneously in the right flank, and serial arterial blood samples were taken for 3 h.[1] The dimensions of the raised wheal were measured immediately after injection and at the end of the 3 h. In a separate set of pigs, the skin at the injection site was transected to determine the thickness of the raised wheal. Blood samples were sent to the Center for Anti-Infective Research and Development at Hartford Hospital to determine the cefazolin concentration using high-pressure liquid chromatography.

Pharmacokinetic analysis

All calculations were first performed separately for each pig and then averaged. Non-compartmental analysis was performed. The elimination rate constant was calculated by linear regression to the semi-log plot of the terminal phase of the serum concentrations. Area under the curve (AUC) was calculated using the linear trapezoidal rule until the final measured concentration. The final concentration divided by the elimination rate constant was added to this. Bioavailability was determined by comparing with the results described by Kilbaugh *et al.*,[15] who determined the AUC for IV administration of cefazolin in a piglet to be 5220 μg × min/mL.

[1] Of note, two of the four pigs had either massage or ultrasound applied to the injection site for a short period, which did not obviously change the rate of drug absorption.

Results

Immediately after injection, the skin at the injection site had a wheal that measured on average 5.4 × 4.8 cm corresponding to an area of 80 ± 3 cm^2. After 3 h, this was reduced to 4.8 × 4.5 cm, corresponding to a 14% reduction in area to 68 ± 13 cm^2. The thickness of the subcutaneous tissue at the injection site also decreased by 20% from an average of 2.1 cm at the start to 1.7 cm 3 h later. Based on the amount of cefazolin injected and the volume of the wheal, the estimated average concentration in the local tissue immediately after injection was 1200 μg/mL. Serum cefazolin was readily detectable after subcutaneous injection (Fig. 1). The pharmacokinetic parameters were determined based on the measured concentration profiles (Table 1). Maximum serum concentrations of cefazolin were achieved 42.6 ± 2.0 min after the time of injection, with a peak concentration of 18.8 ± 7.4 μg/mL. The elimination rate constant was 0.0033 ± 0.0016 min^{-1}, and the half-life was 266 ± 149 min. The AUC was 4940 ± 1030 μg × min/mL. The relative bioavailability of subcutaneous injection was 95% + 5%/−20%.

Discussion

We describe the pharmacokinetics of subcutaneous administration of cefazolin. Kilbaugh *et al.*[15] have previously described the pharmacokinetics of IV administration of cefazolin in a piglet model using the same drug dosage. When compared with the results described by Kilbaugh *et al.* the subcutaneous route shows a lower maximum serum

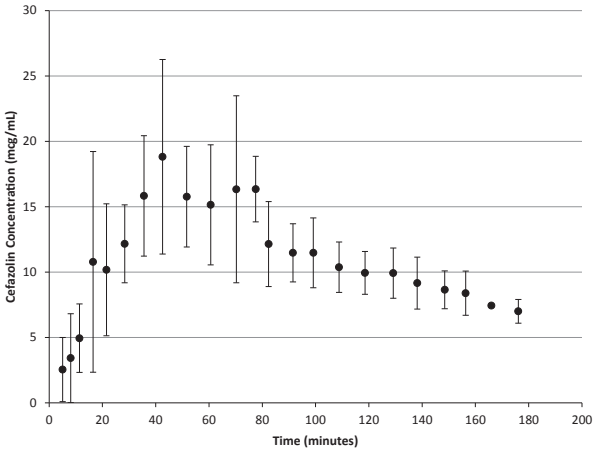

Fig. 1 – Serum concentrations of cefazolin after subcutaneous injection at time t = 0.

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