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Research Article

Examination of Cefazolin Plasma Levels in Cardiac Surgery under a Revised Dutch Dosing Regimen

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- Cefazolin
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Abstract

Introduction: Cefazolin is the first choice antibiotic prophylaxis during cardiac surgery and is widely used to prevent deep sternal wound infections (DSWI). Recently, the Dutch guideline has been changed where the cefazolin dose given at the onset of cardiopulmonary bypass (CPB), has been removed and the postoperative dosages are both halved. The aim of the study is to assess if adequate cefazolin plasma levels are obtained with the new Dutch guideline.

Methods: Twenty-four adults undergoing cardiac surgery with cardiopulmonary bypass (CPB), receiving cefazolin were studied. The main goal is 100% fT >MIC during surgery and epidemiological cutoff is 2 mg/L. During the postoperative phase the goal is 40% fT >MIC. Per patient 9 to 11 blood samples were collected to measure plasma cefazolin concentrations.

Results: During surgery 100% of the measured concentrations were above the ECOFF of 2mg/L. BMI was not significantly associated with unbound cefazolin concentrations. Sex, age, albumin levels preoperative and duration of CPB were also not significantly associated with cefazolin unbound concentration. Redose was significantly associated with higher total plasma concentration. In the postoperative phase 85% were above the ECOFF of 2mg/L.

Conclusion: This study shows that the unbound cefazolin concentration during surgery is 100% above the ECOFF of 2mg/L, though sometimes close to the minimum. In the postoperative period more than 85% was above the ECOFF of 2mg/L.

ABBREVIATIONS

CPB: Cardiopulmonary Bypass; SSI: Surgical Site Infection; ECOFF: Epidemiological Cutoff; BMI: Bodymass Index; MIC: Minimal Inhibitory Concentrations; DSWI: Deep Sternal Wound Infections; EACTS: European Association for Cardio-Thoracic Surgery.

INTRODUCTION

Cefazolin is the first-choice antibiotic for peri-operative prophylaxis during cardiac surgery. This first-generation cephalosporin is widely used to prevent deep sternal wound infections (DSWI) due to Staphylococcus aureus. DSWI is a severe complication occurring in 0.5 to 3.4% of adults undergoing cardiac surgery [1,2], and is associated with increased morbidity and mortality [3].

The recent guideline from the European Association for Cardio-Thoracic Surgery (EACTS), advises to redose cefazolin if the expected duration of the surgical procedure exceeds two half-lives of cefazolin or in case of extensive blood loss [4]. The American guideline, advises differently. The current US guidelines no longer recommend the administration of prophylactic antibiotic doses after wound closure [5].

Recently, the Dutch guideline for use of cefazolin as peri-operative prophylaxis has been changed. The cefazolin dose given at the onset of cardiopulmonary bypass (CPB), has been removed [6]. However, onset of CPB has been shown to decrease cefazolin drug concentrations, most likely due to hemodilution [7,8]. Also, the peri-operative dose administered four hours after the initial dose is reduced from two to one gram, if the remaining duration of surgery is expected to be under three hours, two grams otherwise will be administered. If surgery is completed within four hours, no redose is given during surgery. This decrease in cefazolin dosing could potentially lead to a decreased

unbound cefazolin plasma concentration and values under the targeted minimum concentration during surgery and therefore inadequate prophylaxis.

Approximately 80% of cefazolin is protein bound and thus biologically inactive. In this study unbound plasma cefazolin concentrations were measured in 24 adults undergoing cardiac surgery after implementation of the new Dutch guideline. The aim is to compare the peri-operative and postoperative unbound cefazolin values with the minimum target concentration of 2 mg/L (SWAB guideline) [6], to examine the cefazolin plasma levels with the new Dutch guideline.

MATERIALS AND METHODS

Ethical statement

The study was approved by the Institutional Review Board (IRB), of the Erasmus MC on the 21st of February 2019 (MEC 2018-1519). Twenty-four adult patients who were scheduled for cardiac surgery with the use of CPB were included after written informed consent was obtained.

Patients

Inclusion criteria were: age above 18 years, cardiac surgery with the use of CPB, cefazolin as antibiotic prophylaxis, BMI under 40. Exclusion criteria were: known allergy to cefazolin, treatment for active infection with antibiotics prior to surgery, use of minimal invasive extracorporeal system, eGFR < 35ml/min or ASAT/ALAT > 3 times normal values. In our institution, almost no patients scheduled for cardiac surgery have a BMI over 40. Therefore, we considered these patients outliers and excluded them from the study to ensure a more homogenous population.

Dosing regimen

During induction of anesthesia 2g Cefazolin (Eurocept international, Netherlands), is administered between 0-60 minutes priore to incision. In case of BMI below 40; 4 hours after start surgery a second dose is administered. If the surgery is expected to be finished in less than 3 hours, this second dose is 1mg Cefazolin. If it is expected to be more than 3 hours, the second dose is 2 g Cefazolin. Postoperatively two doses of each 1g Cefazolin are administered; 8hours and 16 hours after last given dose [6].

Study design and procedures

All patients were treated according to standard anesthesiologic and surgical procedures, including the placement of an arterial catheter.

The blood sampling scheme of two milliliters samples, is shown in Figure 1. In case additional perioperative dosing was necessary, samples five and six were taken just before redose and 10-20 min after administration of the dose. Sample number eight was taken during wound closure. In the postoperative phase three samples were collected.

Equilibrium dialysis and bioanalytical method

Blood was collected in ethylenediaminetetraacetic acid (EDTA), coated tubes and stored at 4°C with until processing, with a time range between sample collection and processing from 30 min-12 hours at the research laboratory at the Erasmus MC. Blood was centrifuged (15 min at 3000 rpm), at ambient laboratory temperature and the plasma was transferred to polypropylene cryogenic vials with polypropylene screw caps (Sarstedt Aktiengesellschaft & Co, Nümbrecht, Germany). Samples were stored at -80°C until analysis.

To determine the unbound/free concentrations of cefazolin in the patient plasma samples, plasma samples were first subjected to in vitro equilibrium dialysis in the bioanalytical laboratory of BioNotus (Niel, Belgium). The equilibrium dialysis was carried out on a HTD96b (HTDialysis, USA), using dialysis membranes with a molecular weight cut-off 12-14 kDa. The dialysis experiments were conducted at 37°C against phosphate buffered saline (PBS), for 3 hours (sufficient to reach the equilibrium as indicated by a preliminary experiment). Spiked control samples were included for 50 and 150µg/mL in triplicate.

Upon completion of the equilibrium dialysis, solutions from both compartments (plasma and PBS), were aliquoted. Equal amounts of blank human plasma and blank PBS were added to PBS and plasma aliquots, respectively, in order to process the samples and subsequently analyze them as described below.

The cefazolin concentrations in the samples obtained after dialysis were determined by LC-MS/MS on a Shimadzu UPLC-MS/MS system consisting of a Nexera X2 ultra-fast liquid chromatography (UPLC), system coupled to a Shimadzu LCMS-8050 triple quadrupole mass spectrometer (MS/MS) (Shimadzu, Japan). The bioanalytical method was developed and pre-validated according to the Food and Drug Administration (FDA), and European Medicines Agency (EMA) [9,10] guidelines, and according to the European Bioanalysis Forum (EBF), recommendations. This method was in accordance with the acceptance criteria: the lower limit of quantification (LLOQ), within 20% of the nominal concentration and for other concentrations within 15% of the nominal concentrations. The calibration range of this method was 0.5 - 200µg/mL. Seven calibration curve standards (CCS), were included (0.5, 1, 5, 25, 50, 100 and 200µg/mL). Quality control (QC), samples were included in triplicate for 0.5 (LLOQ), 1.5 (LQC), 50 (MQC), and 150 (HQC) µg/mL. CCS, QC and study samples were processed by protein precipitation and flucloxacillin was used as the internal standard. Prior to each study samples analysis, the seven CCS and four QCs were injected. Afterwards incurred sample reanalysis (ISR), was performed and the criteria of less than 20% difference was met for 2/3 of the samples that were re-analyzed. The cefazolin concentrations measured in the PBS samples obtained after dialysis represent the free plasma cefazolin concentrations.

Sample size

Due to lack on literature on this topic a formal sample size calculation or power analysis was not considered feasible. Fifty percent had a BMI under 25 (kg/m2), and the other fifty percent over 25 (kg/m2), to give a representative sample from the general population, to ensure a good distribution among the two different BMI groups to see the effect of BMI

Targeted minimum concentration

In published literature, a variation of minimal inhibitory concentrations (MIC), were reported. In general a concentration of 2 mg/L is accepted to prevent wound infections with the main

pathogen *S. aureus* [6,11,12]. During surgery the concentration needs to be above the targeted concentration of 2mg/L 100% of the time (100% fT >MIC), and in the postoperative phase 40% is sufficient. The lowest in vitro concentration that prevents visible growth (observed by the unaided eye), in a standardized medium over 18+/-2 h, at 34-36°C using a standardized inoculum [13], is defined as the MIC. These concentrations are 2-fold dilutions from 1 mg/L and thus the MIC represents an endpoint measurement that results from growth and bacteriostatic/bactericidal effects over time. A routine MIC measurement cannot be compared directly with any in vivo concentration. The accuracy for measurements of an MIC is not very high due to biological variation within one strain, between different strains and variation in assay used in different laboratories. Given previous mentioned challenges, MICs need to be considered a value that is a member of a probability distribution and are presented as the epidemiologic cutoff (ECOFF) [14]. The ECOFF is the upper end of the wild-type distribution (i.e. highest MIC for isolates devoid of phenotypically detectable resistance)[15,16]. The EUCAST website provides a list of these ECOFF values. The minimum target for *S. aureus* is therefore 2mg/L [17,18].

Statistical analysis

SPSS version 25 (IBM corporation, 2017), was used for the statistical analysis. Patient characteristics were summarized using descriptive statistics. Categorical data were compared using the X2 or Fisher's exact test when appropriate. Normally distributed continuous variables were compared using the Independent samples T-test.

R (Rstudio, version 3.6.1, 2019), was used to do an additional analysis for continuous repeated measurements of the cefazolin concentrations using mixed-models with random intercepts and time slope for patients for the intraoperative and postoperative period.

Model assumptions were checked and valid after log transformation. A more elaborate explanation of mixed models is provided in supplementary text 2.

RESULTS

Twenty-four patients were included from March until April 2019. The mean age was 64 years, 77% male, the mean BMI was 22.4 kg/m2 in the group with a BMI below the 25. In the group with a BMI above 25, the mean age was 63 years, 73% male and the mean BMI was 28.3 kg/m2. In both groups, valve repair was the most common type of surgical procedure. A summary of the patient characteristics is shown in Table 1.

A total of 227 samples were collected for the unbound cefazolin concentrations. The unbound cefazolin concentrations were measured in 24 patients (Figure 1). During surgery trough unbound cefazolin plasma concentrations were all above the ECOFF of 2 mg/L. There are two timepoints were there are plasma concentration near the minimum targeted concentration eg, timepoint 5, before redose intra-operatively if administered and timepoint 8, during wound closure. After additional analysis with mixed models BMI (P= 0.8) was not significantly associated with unbound plasma concentrations. After stratification per BMI group (Figure 2), sex (P= 0.8), age (P= 0.2), albumin preoperative (P= 0.8), and duration of CPB (P= 0.8), were also not significantly associated with cefazolin unbound concentrations in two different models. Redose (P<0.001), was significantly associated with higher cefazolin concentrations (Figure 3).

Table 1: Patient Characteristics.

Patient characteristics (n)	BMI <25 (kg/m2) (13)	BMI >25 (kg/m2) (11)
Sex (male) (n, %)	10(77)	8 (73)
Age (years, mean, sd)	64(15)	63(16)
Ethnicity (n, %) Caucasian African Asian Other	11(84) 1(8) - 1(8)	10(91) 1(9) -
Weight (kg, mean, sd)	69.8 (15.9)	89(20.9)
BMI ((kg/m2) , mean, sd)	22.4(2.5)	28.3 (2.7)
Medical history (n, %) Hypertension Angina Diabetes mellitus Hypercholesterolemia Previous cardiac surgery	5 (38) 3 (23) - 1 (8) 1 (8)	5 (45) 1 (9) 1 (9) 2 (18) 1 (9)
Surgical procedure (n, %) CABG Valve repair Arch replacement ASD 2 closure Combined procedure	3 (23) 4 (30) 2 (15) 1 (8) 3 (23)	3 (27) 5 (46) - - 3 (27)
Extra dose administered (n,%))	4(33)	6 (50)
Duration of surgery (minutes, mean, sd)	249 (91)	252 (93)
CPB runtime (minutes, mean, sd)	127 (38)	146 (73)

Abbreviations: CPB: cardiopulmonary bypass; BMI: Bodymass index; CABG: Coronary artery bypass grafting; ASD: Atrial septal defect

In the postoperative period the unbound cefazolin concentrations were above the ECOFF of 2mg/L 85% of the time. The cefazolin unbound concentration is significant above the 2mg/L till 497 minutes after end of surgery. On average 775 minutes after end surgery the concentrations reaches levels below the targeted minimum concentration of 2mg/L. BMI (P= 0.8) was not significantly associated with unbound plasma concentrations. Sex (P= 0.7), age (P= 1) and albumin postoperative (P= 1) were also not significantly associated with cefazolin unbound concentrations.

The unbound cefazolin concentration was below 2 mg/L 10 times in 9 patients, all in the postoperative phase. There was no significant association between covariates and a concentration below the 2mg/L (Table 2).

DISCUSSION

This study evaluates the new Dutch protocol for cefazolin prophylaxis during cardiac surgery in adults. Our primary question was if the changed dosing scheme decreased the cefazolin concentration to below the minimum target value. Current antibiotic regimen according to the recently implemented quidelines resulted in adequate cefazolin concentration in all patients.

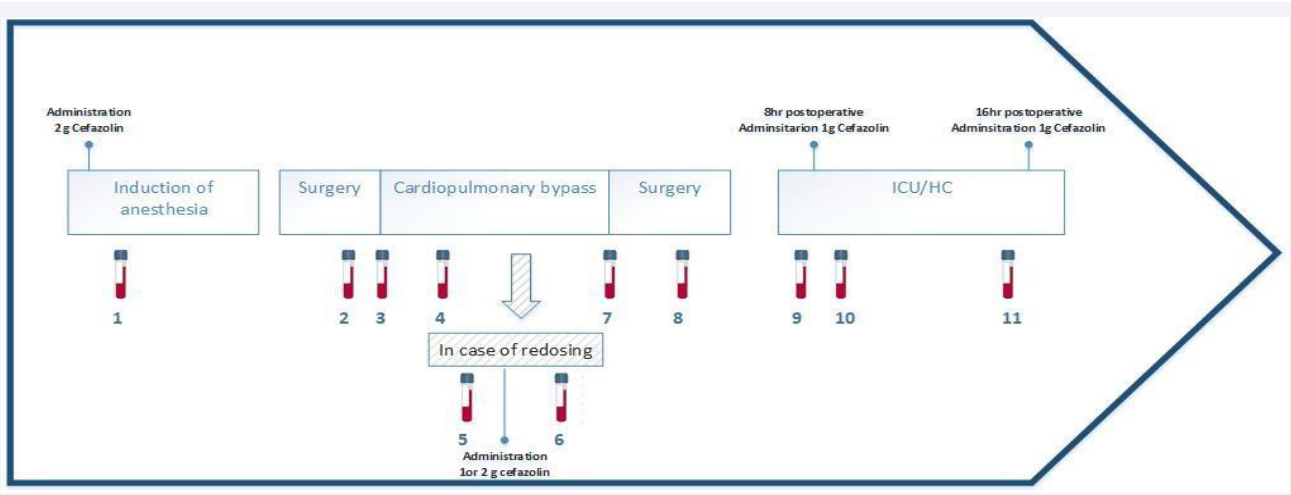

Figure 1 Study overview with timing of cefazolin administration and blood sampling. Blood sampling: 1-10 min after administration of 2 grams cefazolin (1), before cannulation of CPB (2), right after start CPB (3) and 30-40 min after start CPB (4). In case surgery duration was longer than 4 hours, a redose was given and sample 5 (predose) and 6 (10-20 min after dosing) were drawn. Other samples: during weaning from CPB (7) and during sternal wound closure (8), in the postoperative phase 15 minutes before (9) and 10-60min after 8-hours postoperative dose (10) and 15 min before 16-hours postoperative dose (11).

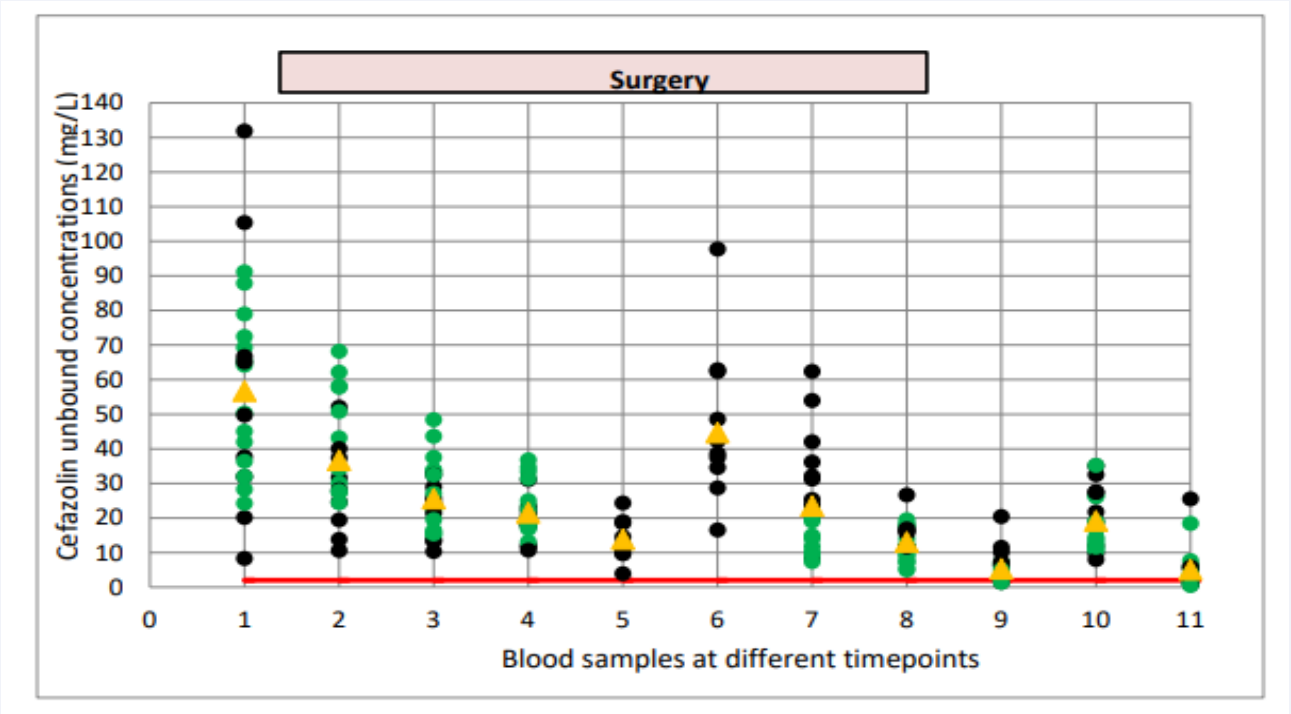

Figure 2 Unbound cefazolin serum concentrations at different time points. Blood samples were taken at 9 to 11 time points. Black dots denote the patients who did receive a redose intra- operative and sample 5 and 6 were taken. The green dots denote the patients, whom did not receive a redose intra-operative. Yellow triangles denote the median values, the red line denotes the ECOFF of 2 mg/L. Intervals between time points on the x-axis are not uniform. The intra-operative period is marked.

From literature, the ECOFF for common pathogens in cardiac surgery is often considered to have at least a value of 2 mg/L. The American guideline on peri-operative antibiotic prophylaxis states that the antimicrobial agents should be administered at the right time to provide adequate serum and tissue concentration exceeding the ECOFF for the probable organism associated with the procedure, at the time of incision and the duration of surgery [19]. The EACTS guideline states that most pathogens isolated from patients with SSI are gram positive bacteria [4]. Calic et al., used a MIC of 8 mg/L corresponding with a total concentration of 40 mg/L assuming the targeted minimum concentration needs to be 4 times the MIC of 2mg/L for maximal bactericidal

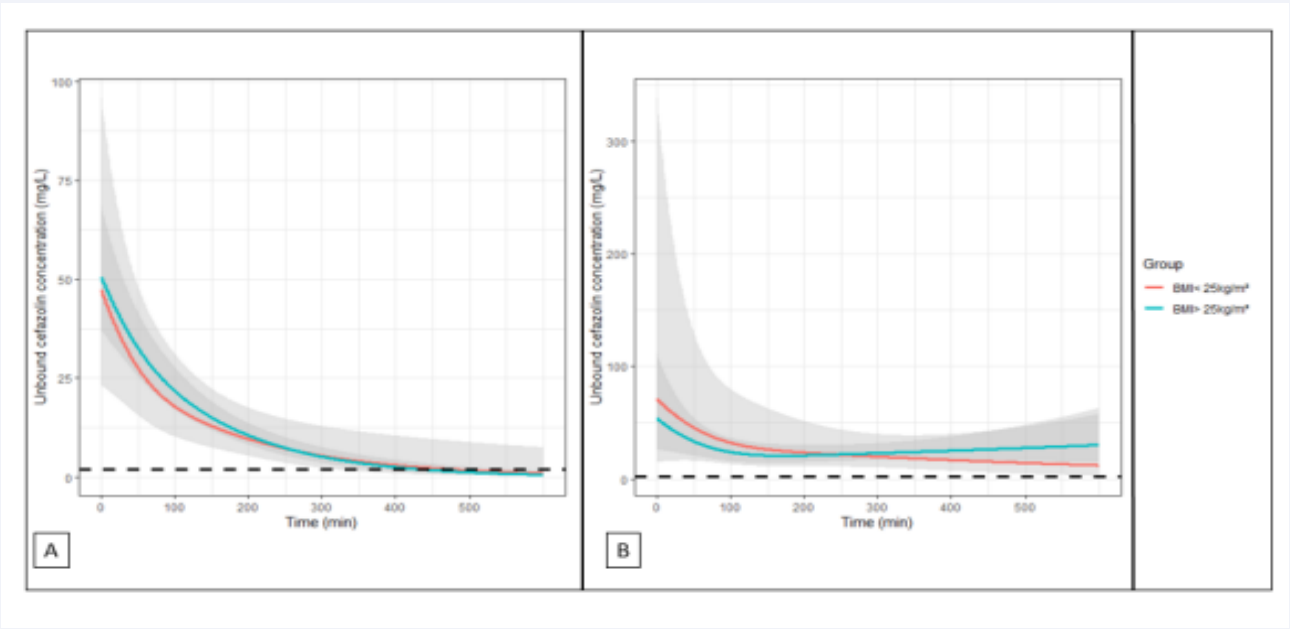

Figure 3 A) Unbound Cefazolin serum concentrations over time during surgery for 14 patients who did not receive a second perioperative dose. B) Unbound Cefazolin serum concentrations over time during surgery for 10 patients who did receive a second perioperative dose. Stratified per BMI below 25 and above 25. The grey ribbon denotes 95% confidence interval. The dashed line denotes the ECOFF of 2mg/L.

Table 2: Univariate Poisson analysis of subject and surgery related variables for unbound cefazolin concentration during study period.

	Unbound cefazolin concentrations <2mg/L	
Variables	***Estimates***	***P***
BMI group	-0.41 (-1.76, 0.85)	*0.5*
Pre-operative albumin level	0.11 (-0.08, 0.36)	*0.6*
Duration surgery	-0.009 (-0.02, 0.0006)	*0.1*
Duration CPB	-0.02 (-0.04, -0.003)	*0.06*
Age	-2.34 (-2.46*10^-15, 2.38*10^-15)	*0.8*
Sex	-1.17 (-4.08, 0.50)	*0.3*

Abbreviations: CPB: cardiopulmonary bypass; BMI: Bodymass index;

effect. The authors reported total concentrations and observed that almost 10% of samples taken at closure were below 40 mg/L, as were almost 40% of intraoperative trough levels at the time of redosing [12]. In our cohort all cefazolin plasma concentrations during the intraoperative period were above the targeted minimum concentration of 2mg/L. However some patients have concentrations very close to the targeted minimum concentration in this critical period. In previous research lower body weight and shorter duration of surgery were significantly associated with cefazolin concentration <40 mg/L at wound closure, probably due to decreased cefazolin administration at time of redosing.[12] This lack of redosing, or decreased cefazolin dosage could also account for our results. In the current protocol, a redose is administered at 4 hours after initial dose pre-operative of 2 grams, eg 1 gram if expected to last <3 hours, 2 grams if expected to last over 3hours. In our cohort duration of CPB was not significantly (P= 0.06) associated with cefazolin unbound concentrations below the ECOFF of 2mg/L and all concentrations during surgery were above 2mg/L.

We also expected to see a difference in the cefazolin concentrations between patients in the different BMI groups (< 25 vs 25-40 kg/m2). In literature, results on interactions between bodyweight and cefazolin concentration are inconsistent. Calic et al., showed that lower body weight is significantly associated with lower cefazolin concentrations at wound closure. Others report that bodyweight is the strongest predictor of volume of distribution and unbound cefazolin concentration reduces with increasing body weight [20]. Van Kralingen et al., showed that unbound cefazolin concentrations at 240 min of surgery were not correlated with total bodyweight. These studies were performed in morbidly obese patients. We did not include patients with an BMI >40 kg/m2, which could account for the differences between our findings and the literature.

Measuring unbound cefazolin concentration in plasma only gives an indication of the efficacy. The actual targeted minimum concentration needs to be achieved in the tissue. Howard et al showed that the unbound fraction of cefazolin in plasma

correlated well with the interstitial fluid [21]. Brill et al., showed that tissue concentration of cefazolin was decreased in morbidly obese patients, requiring adjusted dosing scheme [20]. Andreas et al., showed in patients scheduled for CABG a significant lower subcutaneous plasma concentration after left mammary artery harvesting compared to surgically non-affected presternal right sides. Based on this we can assume that the patients in our cohort (BMI< 40 kg/m2) attained sufficient tissue concentrations.

A major limitation in our study is the small sample size and we did not include morbid obese patients (BMI > 40 kg/m2), in the Netherlands we hardly have these type of patients. However our study population is an adequate representation of the cardiac surgical patients in the Netherlands.

It is often stated that the target concentration needs to be maintained until 24 hours after surgery. It has already been shown that prophylaxis up to 48 hours is not necessary [4]. The most important moment for adequate tissue and serum cefazolin concentration is during wound closure [20]. From microbiologic point of view 100% fT >MIC is not necessary in the postoperative period because manipulation of the surgery is finished and a beginning infection is treated. As treatment 40% fT >MIC should be sufficient. This is based on effectivity studies in mice where 30 to 40% 100% fT >MIC to produce a net bacteriostatic effect [22,23]. All of our patients maintained adequate plasma levels during wound closure, all were above the ECOFF of 2mg/L. In the postoperative period 85% was above the ECOFF of 2 mg/L for *S. aureus*. However there are more bacteria that can cause a surgical site infection. The second most common bacteria to cause DSWI after cardiac surgery are Gram-negative bacilli [24-26], e.g. *E.coli* which has a higher ECOFF of 4mg/L. Furthermore, if an infection occurs with gram-negative bacilli, cefazolin is not the choice of antibiotic for treatment. In our study we used the ECOFF of 2mg/L, because this is the most common pathogen *S. aureus*. This confirms that the current guideline is adequate for *S. aureus*. Our study was not adequately powered to detect an increase in surgical site infection in our population.

CONCLUSION

Our study investigated unbound cefazolin concentration in adult patients undergoing cardiac surgery, after introduction of the new Dutch protocol for antibiotic prophylaxis. We found that cefazolin concentration remained above the ECOFF of 2mg/L during surgery, though sometimes close to the minimum. In the postoperative phase the cefazolin concentration was above the ECOFF 85 % of the time. In the near future we aim to identify patient and surgery specific factors that influence cefazolin total and unbound concentration during cardiac surgery and go more in depth in the protein binding using population pharmacokinetics.

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CONFLICT OF INTEREST

The corresponding author confirms on behalf of all authors that there have been no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated.

Supplementary 1: Elaborate explanation mixed-models

Continuous repeated measurements are analyzed using mixed-models with random intercepts and time slope for patients. The models are visualized by effect plots.

Spline function

A spline is a function with knots (cut points) that cut data in several pieces, or in others words: A piece-wise polynomial. Using this function one can compute a regression coefficient for e.g. the first part of the data and de second part, using 1 knot.

Models with only the time effect

Natural splines as fixed and random effects for time were added to establish flexibility, starting with 2 knots to zero knots. In order not to lose interpretability of splines in random and fixed effect, the statistical models always contained the same number of knots in random as fixed effects. Model performance for different number of splines were compared using AIC and BIC, and the model with the lowest AIC and BIC was chosen. In case of disagreement of AIC and BIC; estimated longitudinal evolution was plotted in 20 random patients and the most suitable evolution was chosen, taking into account smoothness of the line. Effect plots are truncated when <10% of the data/patients remained in the study, or when remaining patients dropped below 5. QQ-plots of standardized residuals were inspected to determine if model assumptions were violated.

Models with time, another covariate and their interaction

All models contained time, the covariate of interest and their interaction term as independent variables. The interaction term was included in order to asses difference courses over time. The method of choosing the number of knots in the spline function for time is described above.

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