Optimal dosage of cefmetazole for intraoperative antimicrobial prophylaxis in patients undergoing surgery for colorectal cancer

Atsushi Tomizawa 1*, Takatoshi Nakamura 2, Toshiaki Komatsu 1, Hiroshi Inano 1, Rumiko Kondo 1, Masahiko Watanabe 2 and Koichiro Atsuda 1

Abstract

Background: Few studies have reported the dosage of cefmetazole (CMZ) for intraoperative antimicrobial prophylaxis in patients underwent surgery for colorectal cancer. We therefore examined the optimal intraoperative dosage of CMZ according to pharmacokinetic/pharmacodynamic (PK/PD) theory in patients who undergoing surgery for colorectal cancer.

Methods: The study group comprised 23 patients with colorectal cancer who underwent surgery, using CMZ as antimicrobial treatment to prevent postoperative infection. CMZ was administered intravenously within 60 min before surgery. PK/PD analysis was performed by population pharmacokinetic analysis and Monte-Carlo simulation.

Results: The final population pharmacokinetic parameters of CMZ were as follows: CL CMZ = 0.0704 × creatinine clearance (Ccr) and Vd CMZ = 0.163 × body weight (Bw). In patients with a Ccr of ≥90 to <130 mL/min, the probability of achieving concentrations exceeding MIC was 52.9 to 82.2% at 2 h after the initial dose and less than 20% at 3 h after the initial dose.

Conclusions: Additional doses of CMZ should be given every 2 h in patients with a Ccr of ≥90 to <130 mL/min, every 3 h in those with a Ccr of ≥50 to <90 mL/min, and every 4 to 5 h in those with a Ccr of ≥10 to <50 mL/min.

Keywords: Cefmetazole, Colorectal surgery, Antimicrobial prophylaxis, Population pharmacokinetics

Background

Cefmetazole (CMZ) is a cephamycin’s antibiotics developed in Japan that has high antibacterial activity against gram-negative and anaerobic bacteria. It is widely used for antimicrobial prophylaxis (AMP) in patients undergoing lower gastrointestinal surgery [1].

Treatment schedules for AMP have been based on the Centers for Disease Control and Prevention guidelines [2], the recommendations of the Surgical Infection Prevention Guideline Writers Workgroup meeting [3], and recent collaborative guidelines issued by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Surgical Infection Society, and the Society for Healthcare Epidemiology of America [4]. A general consensus has also been reached in Japan. However, very few studies have evaluated the pharmacokinetics of CMZ during surgery for colorectal cancer and reported the optimal intraoperative treatment schedule for CMZ, including the timing of additional doses.

We studied the pharmacokinetics of CMZ during surgery in patients with colorectal cancer to determine the optimal dosage of CMZ on the basis of pharmacokinetics and pharmacodynamics.

* Correspondence: tomy@kitasato-u.ac.jp
1Department of Pharmacy, Kitasato University Hospital, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan
Full list of author information is available at the end of the article

© The Author(s), 2017. Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Methods

Data source
The study group comprised 23 patients who underwent surgery for colorectal cancer and received CMZ for AMP between November 2008 and December 2010. Patients who underwent emergency surgery, those with ileus, and those who were receiving dialysis were excluded.

As for the treatment schedule, 1 g of CMZ was intravenously administered over the course of 5 to 10 min after the induction of anesthesia and within 60 min before the surgical incision. Subsequently, 1 g of CMZ was additionally given every 3 h. In principle, blood samples were collected at the start of surgery, on completion of the anastomosis, immediately before additional doses of AMP, and after abdominal closure.

Assay of cefmetazole concentrations
Serum CMZ concentrations were measured by high-performance liquid chromatography (HPLC). After the completion of surgery, blood samples were centrifuged at 3000 rpm for 10 min, and the serum supernatant was preserved by freezing at −80 °C until assay. At the time of assay, 200 μL of serum was combined with 90 μL of a deproteinizing agent (1 M HClO2), and the mixture was centrifuged at 1000 rpm and 4 °C for 5 min. The obtained supernatant was filtered through a 0.45-μm syringe filter, and 50 μL of the filtrate was injected into a chromatograph. The HPLC column temperature was 25 °C, with an ultraviolet absorption wavelength of 256 nm. The mobile phase was prepared by combining 800 mL of 50 mM phosphate buffer (pH 4.5) with 200 mL of acetonitrile. The detection limit was 0.5 μg/mL.

Pharmacokinetics model
Population pharmacokinetic analysis of CMZ was performed with the use of a nonlinear mixed effect model (NONMEM) program (version VI, level 1.0). For the pharmacokinetic model, we used predictions for population pharmacokinetics (PREDPP) subroutines with a linear one-compartment model (ADVAN 1 and TRANS 2) to estimate the pharmacokinetic parameters of the volume of distribution (Vd_CMZ) and clearance (CL_CMZ).

The inter-individual variability of the pharmacokinetic parameters was assessed using an exponential error model according to the following eq (1):

\[ P_j = P \times \exp(\eta_j) \] (1)

Where \( P_j \) is parameter value of the j-th subject, \( P \) is the estimated population mean, and \( \eta_j \) is a random variable with a mean of 0 and a variance of \( \sigma^2 \).

The intra-individual variability of the parameters was assessed using a proportional error model according to the following eq (2):

\[ C_{ij} = C_{\text{pred},ij} \times (1 + \epsilon_{ij}) \] (2)

Where \( C_{ij} \) and \( C_{\text{pred},ij} \) denotes observed and predicted concentrations for the j-th subject at i-th time, and \( \epsilon_{ij} \) is a random intra-individual error which is normally distributed with mean 0 and variance \( \sigma^2 \).

Covariate analysis
The covariates of patients were performed for their influence on CMZ pharmacokinetic parameters as followed; age (Age), gender (Gender), body weight (Bw),

| Parameter          | Numbers | Mean ± SD | Range |
|--------------------|---------|-----------|-------|
| Gender (male/female) | 18 / 5  |           |       |
| Cancer (colon / rectum) | 14 / 9  |           |       |
| Stage (I/II/III/IV)  | 10 / 6 / 6 / 1 |       |       |
| Procedure (lap*/open) | 13 / 10 |           |       |
| Age (years)         | 69 ± 10 | 41–84     |       |
| Body weight (kg)    | 63.7 ± 9.9 | 47.5–89.0 |       |
| Body mass index (kg/m²) | 24.1 ± 4.1 | 19.0–34.3 |       |
| Serum creatinine (mg/dL) | 0.84 ± 0.17 | 0.57–1.3 |       |
| Creatinine clearance (mL/min) | 73.9 ± 21.7 | 47.2–126.3 |       |
| Serum albumin (g/dL) | 3.8 ± 0.4 | 3.3–4.6   |       |
| Operation time (min) | 238 ± 73 | 140–430   |       |

\* lap laparoscopic procedure
clinical pathological stage (Stage), serum creatinine (Scr), creatinine clearance (Ccr), serum albumin (Alb), and operative procedure (Procedure). Operative procedures were divided into open surgery and laparoscopic surgery. Ccr was calculated using the Cockcroft-Gault equation.

The influence of continuous covariates on the pharmacokinetic parameter was modeled according to the following eqs (3, 4):

\[
P = \theta p + \theta c \times (\text{covariance})
\]

\[
P = \theta p \times \theta c^{(\text{covariance})}
\]

The significance of the influence of covariates was evaluated by the change of \(-2\) log likelihood (the minimum value of the objective function: OBJ).

Table 2

| Parameter       | Fixed effects model                              | OBJ    | \(-2\) l.l.d. | \(p\)-value |
|-----------------|--------------------------------------------------|--------|---------------|-------------|
| \(CL\)          | \(\theta_1\)                                     | 491.305|               |             |
|                 | \(\theta_1 + \theta_2 \times \text{Ccr}\)       | 476.461| \(-14.844\)   | 0.001       |
|                 | \(\theta_1 + \theta_2 \times 1 / \text{Scr}\)   | 486.958| \(-4.347\)    | N.S.        |
|                 | \(\theta_1 \times \theta_2^{\text{Gender}}\)   | 486.934| \(-4.371\)    | N.S.        |
|                 | \(\theta_1; \text{Age } \geq 65, \theta_2; \text{Age } < 65\) | 491.291| \(-0.014\)    | N.S.        |
|                 | \(\theta_1; \text{Alb } \geq 3.8, \theta_2; \text{Alb } < 3.8\) | 491.305| 0             | N.S.        |
|                 | \(\theta_1 + \theta_2 \times (1 + (4 - \text{stage}))\) | 490.054| \(-1.251\)    | N.S.        |
|                 | \(\theta_1 \times \theta_2^{\text{Procedure}}\) | 491.074| \(-0.231\)    | N.S.        |
|                 | \(\theta_1 + \theta_2 \times \text{BW}\)       | 489.316| \(-1.989\)    | N.S.        |
| \(Vd\)          | \(\theta_1 \times \theta_2^{\text{Gender}}\)   | 491.295| 0.010         | N.S.        |
|                 | \(\theta_1; \text{Age } \geq 65, \theta_4; \text{Age } < 65\) | 490.189| 1.116         | N.S.        |
|                 | \(\theta_1 + \theta_2 \times \text{BW}\)       | 473.811| 17.494        | 0.001       |

\(-2\) l.l.d.: \(-2\) log likelihood difference

N.S. Not significant

Parameter precision and model stability were estimated for the final model by the bootstrap method [5]. 200 bootstrap samples were reconstructed, and the final model was determined by the 200 bootstrap samples repeatedly tested. The mean and standard error (S.E.) for each estimated parameters calculated normally were compared with those obtained from the original data set.

Evaluation of optimal dosage

A Monte-Carlo simulation [6] was performed 1000 times with the estimated and dispersion values of the population pharmacokinetic parameters, using Microsoft Excel 2010. Estimated serum CMZ concentrations were calculated after 2, 3, 4, 5, and 6 h. On the basis of the minimum inhibitory concentration (MIC) distribution of \textit{Bacteroides fragilis}, the probability of achieving serum CMZ concentrations above the MIC \(80 : \text{MIC attainment rate, was calculated. As for the MIC distribution of Bacteroides fragilis for CMZ, a Japanese surveillance report}

| Parameter          | Estimate | Variability |
|--------------------|----------|-------------|
| \(CL\)             | 0.0704   | 21.0        |
| \(Vd\)             | 0.163    | 8.4         |
| \(CL\)             | 0.0704   | 21.0        |
| \(Vd\)             | 0.163    | 8.4         |

Table 3 Final pharmacokinetic parameter estimates for cefmetazole in patients undergoing colorectal surgery

| Pharmacokinetic Parameters | Estimate | Variability |
|----------------------------|----------|-------------|
| \(CL\) = \theta_1 \times \text{Ccr} \ (L/h) |          |             |
| \(Vd\) = \theta_2 \times \text{BW} \ (L) |          |             |
| \(CL\) = \theta_1 \times \text{Ccr} \ (L/h) |          |             |
| \(Vd\) = \theta_2 \times \text{BW} \ (L) |          |             |

| Parameter          | Estimate | Variability |
|--------------------|----------|-------------|
| \(CL\)             | 0.0704   | 21.0        |
| \(Vd\)             | 0.163    | 8.4         |
| \(CL\)             | 0.0704   | 21.0        |
| \(Vd\)             | 0.163    | 8.4         |

-2 l.l.d.: \(-2\) log likelihood difference

N.S. Not significant
of the antimicrobial susceptibility of clinical isolates of anaerobic bacteria in 2004 was used.

Results

Table 1 shows the demographic characteristics of the patients. Serum concentrations were measured at a total of 86 points. The time course of serum CMZ concentrations is shown in Fig. 1. Ccr was a covariate that significantly influenced CL$_{CMZ}$, and Bw was a covariate that significantly influenced Vd$_{CMZ}$ (Table 2). These factors were integrated into the full model, which was compared with a reduced model. Consequently, the final CMZ population pharmacokinetic estimates were CL$_{CMZ}$ = 0.0704 × Ccr and Vd$_{CMZ}$ = 0.163 × Bw. The calculated interindividual variability (CV%) was 21.0% for CL$_{CMZ}$ and 8.4% for Vd$_{CMZ}$, and the residual variability was 13.5% (Table 3).

On regression analysis of Cp and PRED, a correlation coefficient of $r^2 = 0.8671$ was obtained (Fig. 2a). On regression analysis of Cp and IPRED, a correlation coefficient of $r^2 = 0.9437$ was obtained (Fig. 2b). Weighted residuals (WRES) estimated on the basis of Cp and PRED were almost uniformly distributed within a range of about ±3 when WRES = 0 (Fig. 3). The results of bootstrap validation of the estimated pharmacokinetic parameters are shown in Table 4. The convergence rate was 100% (200/200).

Table 5 shows the probability of attaining predicted serum concentrations above the MIC of Bacteroides fragilis: MIC target attainment rate, according to Ccr and Bw, calculated on Monte Carlo simulation of the population pharmacokinetic parameters. The MIC target attainment rate 3 h after the initial dose of CMZ was 3.39 to 15.6% in patients with a Ccr of ≥90 to <130 mL/min and 90% or higher in patients with a Ccr of 50 to <90 mL/min, irrespective of Bw. In patients with a Ccr of ≥10 to <50 mL/min, the MIC target attainment rate 5 h after the initial dose of CMZ was 81.2 to 90.6%.

Discussion

Outside of Japan, cefoxitin and cefotetan are used as perioperative antimicrobial prophylaxis in patients who undergoing surgery for colorectal cancer [2–4]. Because these drugs cannot be used in Japan, however, CMZ, which is also a cephemycin’s antibiotics, is widely employed. Few studies have examined the optimal dosage of CMZ in patients under surgery, including the initial dose of CMZ was 52.9 to 82.2% in patients with a Ccr of ≥90 to <130 mL/min and 90% or higher in patients with a Ccr of 50 to <90 mL/min, irrespective of Bw. In patients with a Ccr of ≥10 to <50 mL/min, the MIC target attainment rate 5 h after the initial dose of CMZ was 81.2 to 90.6%.
intraoperative administration of additional doses. We believe that it is extremely important to assess the optimal dosage of CMZ on the basis of PK/PD theory.

The CL CMZ obtained on population pharmacokinetic analysis was dependent on Ccr, and Vd CMZ was dependent on Bw. These findings were considered reasonable because more than 85% of CMZ is excreted as the unchanged compound in the urine, and excretion is mainly renal. A CL CMZ of 7.04 L/h (Ccr : 100 mL/min) and a Vd CMZ of 10.4 ± 1.6 L (Bw : 47.5 to 89.0 kg) were generally consistent with the results of Borin et al. (CL : 6.96 L/h, Vd : 11.9 ± 4.2 L) [7] and Wong-Beringer et al. (Vd : 0.14 to 0.28 L/kg) [8].

Finally, models were prepared for estimating CL CMZ on the basis of Ccr, and Vd CMZ on the basis of Bw. These data can be obtained from serum chemical analysis before surgery, thus resulting in a clinically appropriate and practical model.

On diagnosis of the final model, regression analysis showed that a high correlation coefficient was obtained between observed serum CMZ concentrations and predicted CMZ concentrations based on population mean parameters, with a high regression coefficient, suggesting that predicted concentrations based on population mean parameters were good. On bootstrap validation, the mean bootstrap values approximated the final model values. The robustness was 100% (200/200) on normal completion of calculation, thus demonstrating the internal validity of the population parameters.

When the optimal treatment schedule for CMZ was assessed using the obtained population pharmacokinetic parameters, the MIC attainment rate at 2 h after initial treatment was 52.9 to 82.2% in patients with a Ccr of ≥90 to <130 mL/min irrespective of Bw. In contrast, the MIC attainment rate was less than 20% at 3 h after initial treatment. This finding suggested that additional doses should be given every 2 h after the initial dose in patients with a Ccr of ≥90 to <130 mL/min. The timing for additional doses of CMZ in patients with a Ccr of ≥90 to <130 mL/min is considered consistent with the recommendations of current guidelines [3, 4].

However, the essential goal of AMP is to decrease bacterial counts to a level that does not cause infection, given the susceptibility of the individual patient to infection. Therefore, treatment schedules should be adjusted according to the Bw and renal function of individual patients, rather than indiscriminately giving additional treatment to all patients.

Our results suggest that additional dose of CMZ should be given every 2 h in patients with a Ccr of ≥90 to <130 mL/min, every 3 h to those with a Ccr of ≥50 to <90 mL/min, and every 4 to 5 h in those with a Ccr of ≥10 to <50 mL/min. Our limitation was the low number of renal failure (Ccr of <50 mL/min) patient (n = 1). Therefore our recommended dosage should be adjusted to each individual clinical situation and care must be taken with patients to Ccr of <50 mL/min.

Further studies of larger number of patients are required to confirm whether our results are consistent with external data and to assess the relation between the MIC attainment rate and the risk of surgical site infection.

### Table 4 Bootstrap validation of the estimated pharmacokinetic parameters

| Parameter | Final model<sup>a</sup> (mean ± S.E.) | Bootstrap<sup>b</sup> (mean ± S.E.) | Difference<sup>c</sup> |
|-----------|-------------------------------------|-------------------------------------|------------------------|
| θ<sub>1</sub> (CL) | 0.0704 ± 0.0029 | 0.0703 ± 0.0029 | −0.001% |
| θ<sub>2</sub> (Vd) | 0.163 ± 0.0054 | 0.164 ± 0.0057 | 0.6% |
| ω<sub>CL</sub> | 0.210 ± 0.0137 | 0.202 ± 0.0035 | −3.8% |
| ω<sub>Vd</sub> | 0.084 ± 0.0053 | 0.070 ± 0.0377 | −16.7% |
| σ | 0.135 ± 0.0045 | 0.133 ± 0.0015 | −1.5% |

<sup>a</sup>Obtained from the original data set
<sup>b</sup>Calculated from 200 bootstrap replications
<sup>c</sup>={(Bootstrap value - Final model value)/Final model value} × 100

### Table 5 The target attainment rate above MIC80 of Bacteroides fragilis calculated on Monte Carlo simulation

| Bw (kg) | Ccr (mL/min) | 2 h | 3 h | 4 h | 5 h | 6 h |
|---------|--------------|-----|-----|-----|-----|-----|
| ≥90 to <130 | 52.87% | 3.39% | 0.00% | 0.00% | 0.00% |
| ≥40 to 50 | 91.24% | 57.89% | 19.42% | 3.45% | 0.37% |
| ≥10 to <50 | 98.66% | 96.67% | 92.96% | 81.20% | 66.08% |
| ≥90 to <130 | 72.44% | 8.56% | 0.14% | 0.00% | 0.00% |
| ≥50 to <90 | 92.17% | 72.40% | 33.66% | 8.28% | 2.33% |
| ≥10 to <50 | 98.19% | 96.71% | 93.43% | 88.53% | 74.18% |
| ≥90 to <130 | 82.16% | 15.57% | 1.58% | 0.00% | 0.00% |
| ≥60 to 70 | 92.69% | 81.51% | 44.25% | 15.74% | 4.78% |
| ≥10 to <50 | 97.27% | 96.06% | 93.16% | 90.56% | 79.45% |
Conclusions
We studied to determine the optimal dosage of CMZ during surgery in patients with colorectal cancer.
Our results suggest that additional dose of CMZ should be given every 2 h in patients with a Ccr of ≥90 to <130 mL/min, every 3 h to those with a Ccr of ≥50 to <90 mL/min, and every 4 to 5 h in those with a Ccr of ≥10 to <50 mL/min.

Abbreviations
AMP: Antimicrobial prophylaxis; Bw: Body weight; Ccr: Creatinine clearance; CL: Clearance; CMZ: Cefmetazole; HPLC: High-performance liquid chromatography; MIC: Minimum inhibitory concentration; OBJ: Objective function; PK/PD: Pharmacokinetic/pharmacodynamic; Vd: Volume of distribution

Acknowledgements
We are indebted to Professor Kazuo Yago, Dr. Hirotugu Okamoto, Ms. Saki Nara for their guidance and cooperation in this study.

Funding
There are no funding sources for this report.

Availability of data and materials
Not applicable.

Authors' contributions
AT wrote the manuscript. AT, TN and TK analyzed and interpreted the patient data regarding for colorectal cancer and pharmacokinetic/pharmacodynamic theory. HI measured cefmetazole concentrations. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Kitasato University Hospital (B10-59: approved on July 24, 2010).

Author details
1Department of Pharmacy, Kitasato University Hospital, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan. 2Department of Surgery, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan.

Received: 23 October 2016 Accepted: 21 December 2016
Published online: 07 January 2017

References
1. Kobayashi M, Takesue Y, Kitagawa Y, Kusunoki M, Suniyama Y. Antimicrobial prophylaxis and Colon Preparation for Colorectal Surgery: Results of a Questionnaire Survey of 721 Certified Institutions in Japan. Surg Today. 2011;41:1363–9.
2. Mangram AJ, Horan TC, Pearson ML, Pearson MR, Silver LC, Jarvis WR, et al. Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control. 1999;27(2):97–134.
3. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis. 2004;38:1705–15.
4. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auswaert PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health-Syst Pharm. 2013;70:195–283.
5. Ette EI. Stability and performance of a population pharmacokinetic model. J Clin Pharmacol. 1997;37(6):486–95.
6. Sheppard CW. Computer simulation of stochastic processes through model - sampling (Monte Carlo) techniques. FEBS Lett. 1969; 2(Supplement1):S14–21.
7. Born MT, Peters GR, Smith TC. Pharmacokinetics and dose proportionality of cefmetazole in healthy young and elderly volunteers. Antimicrob Agents Chemother. 1990;34(10):1944–8.
8. Wong-Beringer A, Corelli RL, Schrock TR, Guglielmo BJ. Influence of timing of antibiotic administration on tissue concentrations during. Am J Surg. 1995;169(4):379–81.