Open Access

SCHOLARENA

SAJ Pharmacy and Pharmacology

RESEARCH ARTICLE

ISSN: 2375-2262

Retrospective Comparative Study to Compare Clinical Efficacy and Safety between Regular Dose and High Dose Cefmetazole Treatments

Yuichi Shibata[1,2], Mao Hagihara[2], Nobuhiro Asai[2], Arufumi Shiota[1,2], Hideo Kato[2], Jun Hirai[2], Yuka Yamagishi[2] and Hiroshige Mikamo[2*]

[1]Department of Pharmacy, Aichi Medical University Hospital, Japan

[2]Department of Infection Control and Prevention, Aichi Medical University Hospital, Japan

[*]**Corresponding author:** Hiroshige Mikamo, MD, PhD, Department of Infection Control and Prevention, Aichi Medical University Hospital, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan, Tel: +810561611842, E-mail: mikamo@aichi-med-u.ac.jp

Citation: Yuichi Shibata, Mao Hagihara, Nobuhiro Asai, Arufumi Shiota, Hideo Kato, et al. (2022) Retrospective Comparative Study to Compare Clinical Efficacy and Safety between Regular Dose and High Dose Cefmetazole Treatments SAJ J Pharm and Pharmacol 8: 102

Abstract

Background: Cefmetazole (CMZ) is a cephamycin antibiotic used in Japan. CMZ dosage regimen, particularly for critically ill patients, remains to be determined. Therefore, we retrospectively compared the clinical efficacy and safety of a high CMZ dose (2 g every 8 h) and regular CMZ dose (2 g every 12 h).

Methods: Here, 143 patients administered CMZ were divided into regular-dose group (62 patients) and high-dose group (81 patients). We investigated the clinical efficacy based on the data of inflammatory markers, such as body temperature, white blood cell count, and C-reactive protein level. The safety of CMZ was evaluated using the Common Terminology Criteria for Adverse Events, version 4.03.

Results: The levels of all inflammatory markers in the high-dose group decreased earlier than those in the regular-dose group. The proportion of patients with alanine aminotransferase (ALT) elevation in the high-dose group was significantly higher than that in the regular-dose group (22.2% vs. 9.7%, $p < 0.05$).

Conclusion: A high CMZ dose was effective in early improvement of inflammation in patients; however, it was associated with a risk factor of ALT elevation. Therefore, we recommended to select the regular CMZ dose (2 g every 12 h) as the patients with general infections and consider to select the high CMZ dose (2 g every 8 h) as the patients with symptoms worsen and normal liver function.

Keywords: Cefmetazole; High Dose; Renal Function; Liver Function

Introduction

Cefmetazole (CMZ) is a cephamycin antibiotic that has been developed in Japan and exhibits high antibacterial activity against gram-negative and anaerobic bacteria. The antibiotic spectrum of CMZ is narrower than that of carbapenems as it does not include *Pseudomonas* and *Acinetobacter* species. Because of this characteristic, CMZ has an advantage over carbapenems and can play an important role in antibacterial stewardship program. Currently, extended spectrum beta-lactamase (ESBL)-producing *Enterobacterales* and carbapenem-resistant *Enterobacterales* are the most concerning pathogens [1]. Infections caused by these organisms are associated with higher mortality [2] and medical cost [3-5]. Currently, the primary standard therapy for bacteremia caused by ESBL-*Enterobacterales* includes only carbapenems [2,6], and therefore, these antibiotics are the most frequently used [7]. However, a previous observational study demonstrated that CMZ, used as a definitive therapy, was effective against bacteremia caused by ESBL-producing *Escherichia coli* (*E. coil*) [8]. Other studies have also demonstrated that CMZ showed similar effects to carbapenems against bacteremia caused by ESBL-producing *E. coli* [9,10]. Hence, CMZ could be a potential candidate alter-native to carbapenems.

In the drug package insert, 1 g CMZ every 12 h is recommended for patients with general infections. However, previous clinical studies recommended a regimen containing 2 g CMZ every 12 h, particularly for treating severe infections such as sepsis, based on the pharmacokinetics (PK)/pharmacodynamics (PD) theory and antibiotic susceptibility of CMZ against clinical isolates [11,12].

The PK/PD parameter of β-lactams, including CMZ, is the percentage of time during which the unbound (free) drug concentration remains above the minimum inhibitory concentration (MIC) of the infecting pathogen (%*f*T >MIC) [13]. In vitro study reported that CMZ possesses time-dependent bactericidal activities against ESBL-producing *E. coli* and is required to achieve %*f*T>MIC ≥ 69.6% for the treatment of ESBL-producing *E. coli* infections [14]. However, an appropriate dosage regimen of β-lactams remains a challenge owing to the altered PK in critically ill patients [15-17]. A larger volume of distribution, caused by fluid resuscitation and capillary leak syndrome, results in subtherapeutic levels of antibiotics [18]. Fluctuations in renal clearance, such as augmented renal clearance or acute kidney injury, can alter anti-biotic concentrations [19]. Therefore, the standard recommended dose of β-lactams in critically ill patients can be associated with increased risk of treatment failure [20-22]. However, a high CMZ dose (2 g every 8 h) has not yet been evaluated for its effectiveness. In this study, we retrospectively compared the efficacy and safety of high and regular doses of CMZ (2 g every 8 h and 2 g every 12 h) in patients.

Patients and Methods

Patients: A total of 143 patients received CMZ treatment at the Aichi Medical University Hospital between December 2014 and February 2021. The inclusion criteria were as follows: age > 18 years and patients who received three or more doses of CMZ. The inclusion criteria were set according to previous reports [23]. Patients receiving CMZ treatments were divided into two groups depending on dosage (2 g CMZ every 12 h (regular-dose group) and 2 g CMZ every 8 h (high-dose group).

Patients who received other antibiotics or antifungal, antiviral, or anticancer drugs were excluded. We collected clinical data of patients, including age, sex, weight, underlying diseases, concomitant medications, infection type, and laboratory data. Additionally, we collected microbiological data if bacteria were detected from the patient. All isolates were collected as part of the standard patient care.

Microbiological Data: Identification and susceptibility tests for isolated organisms were conducted in the Department of Laboratory at Aichi Medical University Hospital. All isolates were tested for susceptibility using the broth microdilution method as described by the Clinical and Laboratory Standards Institute.

Clinical and Microbiological Efficacy. Clinical effectiveness was evaluated using inflammatory markers, such as body temperature, WBC count, and CRP levels, which were assessed at least three days before CMZ therapy initiation as baseline and two weeks after CMZ therapy initiation for clinical efficacy evaluation. The microbiological cure was defined as effective, when bacteria disappeared during and after CMZ therapy. The clinical and microbiological efficacy were evaluated using methods reported by Kato et al.[23]

Safety Evaluation: Renal function was assessed based on Scr levels before initiation and after completion of CMZ therapy. Nephrotoxicity was defined by an increase in Scr levels by 0.5 mg/dL or 50% of the value before CMZ treatment. Liver function was assessed based on T-Bil, AST, ALT, and ALP levels before initiation and after completion of CMZ therapy. Hepatotoxicity was evaluated using Common Terminology Criteria for Adverse Events (CTCAE; version 4.03). Hepatotoxicity was defined by an elevation of more than 1 CTCAE grade in more than one liver enzyme.

Ethics approval and consent to participate

The study was reviewed and approved by the ethics committee of Aichi Medical University (number: 2020-015).

Statistical analysis. Data are expressed as the mean value with a range (minimum–maximum). The statistical significance of the differences was evaluated using the Chi square test for categorical data and Mann–Whitney U test for continuous data. Multiple comparisons of inflammatory markers were made using the Bonferroni/dunnett's test. Statistical analyses were performed using the JMP, version 10.0 (SAS, Tokyo, Japan). Statistical significance of Chi square test and Mann–Whitney U test was set at $p < 0.05$. Statistical significance of Bonferroni/dunnett's test was set at $p < 0.0083$.

Results

Patients: In total, 143 patients were included in this retrospective study (Table 1). The number of patients in the regular- and high-dose groups was 62 and 81, respectively. Significant differences were observed between the two groups with respect to several clin-

	Regular dose	**High dose**	***P* value**
	(N=62)	**(N=81)**	
Age (years)	79.0 (25.0-92.0)	74.0 (20.0-95.0)	0.048 a
Body weight (kg)	79.0 (25.0-92.0)	56.4 (26.5-104.0)	0.005 a
Sex (Male/Female)	31/31	43/38	0.714 b
Used immunosuppressant (%)	16.1 (10/62)	6.2 (5/81)	0.099 c
With diabetes (%)	29.0 (18/62)	28.4 (23/81)	0.933 b
ICT consulting	67.7 (42/62)	92.6 (75/81)	<0.001 b
Duration (days)	6.0 (3.0-55.0)	6.0 (3.0-20.0)	0.768 a
DIC score ≥ 4 (%)	6.5 (4/62)	9.9 (8/81)	0.669 c
qSOFA ≥ 2 (%)	11.3 (7/62)	8.6 (7/81)	0.807 c
BUN (mg/dL)	17.1 (0.5-70.0)	13.4 (3.7-74.8)	<0.001 a
T-Bil (mg/dL)	0.8 (0.3-6.1)	0.8 (0.2-8.1)	0.494 a
Scr (mg/dL)	0.9 (0.3-3.4)	0.7 (0.1-4.0)	<0.001 a
CLcr (mL/min)	46.2 (13.0-166.1)	72.3(11.6-280.3)	<0.001 a
Ccr ≥ 50mL/min (%)	43.5 (27/62)	82.7 (67/81)	<0.001 b
AST (U/L)	28.0 (11.0-726.0)	28.0 (9.0-651.0)	0.435 a
ALT (U/L)	22.0 (6.0-330.0)	23.0 (5.0-291.0)	0.879 a
ALP (U/L)	279.0 (73.0-2165.0)	258.0 (107.0-2308.0)	0.408 a

a; Mann-Whitney U test for continuous data. (Median (min-max))

b; Chi square test for categorical data

c; Chi square test (yates correction) for categorical data

ICT; Infection control team

DIC; Disseminated intravascular coagulation

qSOFA; quick Sequential Organ Failure Assessment

Table 1: Clinical characteristics of patients

ical characteristics. Patients in the high-dose group were younger than those in the regular-dose group (74.0 [20.0–95.0] vs. 79.0 [25.0–92.0], $p = 0.047$). The patients were significantly heavier in the high-dose group than in the regular-dose group. Regarding renal function, creatinine clearance (CLcr) was significantly higher in the high-dose group than in the regular dose group (46.2 [13.0–166.1] vs. 72.3 [11.6–280.3], $p < 0.001$). CLcr was calculated using the Cockcroft-Gault equation [24]. The prediction of creatinine clearance (in ml/min) by the Cockcroft-Gault formula was calculated as (140 − age) × body weight/plasma creatinine × 72 (× 0.85 if female). However, there was no statistical difference in the liver function as well as the duration of CMZ treatment between the two groups (6.0 [3.0–55.0] vs. 6.0 [3.0–20.0], $p = 0.768$). The proportion of the Infection control team (ICT) consulting in the high dose group was significantly higher than regular dose group (67.7% vs. 92.6%, $p < 0.001$). There was no significantly difference in the proportion of the patients with quick Sequential Organ Failure Assessment (qSOFA) ≥ 2 (11.3% vs 8.6%, $p = 0.807$) and disseminated intravascular coagulation (DIC) score (calculated with the JAAM criteria) ≥ 4 (6.5% vs 9.9%, $p = 0.669$) between the both groups.

The proportion of patients with disease based on the infection types is presented in Table 2. The highest proportion of patients had bacteremia (56.5% and 60.5%) in regular-dose and high-dose groups. Further, the proportion of patients based on the clinical isolates is presented in Table 3. The highest proportion of detected clinical isolates was ESBL non-producing *E. coli* (45.2% and 38.3%) in both groups (Table 3). There were no significant differences in the disease and bacterial types between the regular and high-dose groups.

	Total		Regular dose		High dose	
	n	(%)	n	(%)	n	(%)
Infection type						
Bacteremia	84	(66.4)	35	(56.5)	49	(60.5)
Urinary infection	56	(39.2)	31	(50)	25	(30.9)
Respiratory infection	10	(7)	6	(9.7)	4	(4.9)
Gastrointestinal infection	41	(28.7)	14	(22.6)	27	(33.3)
Others	11	(7.7)	4	(6.5)	7	(8.6)

Table 2: Disease type

	Total		**Regular dose**		**High dose**	
	n	(%)	n	(%)	n	(%)
Escherichia coli	59	(41.3)	28	(45.2)	31	(38.3)
Escherichia coli (ESBL)	28	(19.6)	12	(19.4)	16	(19.8)
Klebsiella spp.	26	(18.2)	8	(12.9)	18	(22.2)
Streptococcus spp.	18	(12.6)	7	(11.3)	11	(13.6)
Staphylococcus spp.	11	(7.7)	4	(6.5)	7	(8.6)
Aerococcus spp.	4	(2.8)	2	(3.2)	2	(2.5)
Clostridium spp.	4	(2.8)	2	(3.2)	2	(2.5)
Bacillus spp.	2	(1.4)	1	(1.6)	1	(1.2)
Edwardsiella spp.	2	(1.4)	1	(1.6)	1	(1.2)
Others	20	(14.0)	4	(6.5)	16	(19.8)

ESBL; Extended spectrum β-lactamases

Table 3: Clinical isolates of this study (include duplicate cases) (n=143)

Safety assessment: The changes in clinical data before and after CMZ treatment are presented in Table 4. We examined the changes in total bilirubin (T-bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and serum creatinine (Scr) levels pre- and post-CMZ treatment. The percentage of patients with any substantially abnormal laboratory values after antibacterial treatment were similar in both groups: 19.4% in regular-dose group vs. 29.6% in high-dose group ($p = 0.161$). ALT elevation was the most frequently detected abnormal laboratory parameter in both groups. However, the frequency of ALT elevation in the high-dose group was significantly higher than that in the regular-dose group (9.7% vs. 22.2%, $p < 0.047$). Patients were divided into two groups based on their CLcr (CLcr ≥ 50: normal renal function group and CLcr < 50: abnormal renal function group) before initiation of CMZ treatment. Further, among patients with normal renal function, the proportion of patients with any abnormal laboratory value in the high-dose group was higher than that of patients in the regular-dose group (34.3% vs. 22.2%, $p = 0.366$). However, in the same population, ALT elevation was the most frequently observed in both groups (14.8% for regular-dose group and 26.9% for high-dose group, $p = 0.327$). In contrast, among patients with abnormal renal function, the high-dose group exhibited abnormal laboratory values more frequently than the regular-dose group (17.1% vs. 7.1%, $p = 0.656$). Moreover, ALP and AST elevations were the most frequently observed in the regular and high-dose groups, respectively.

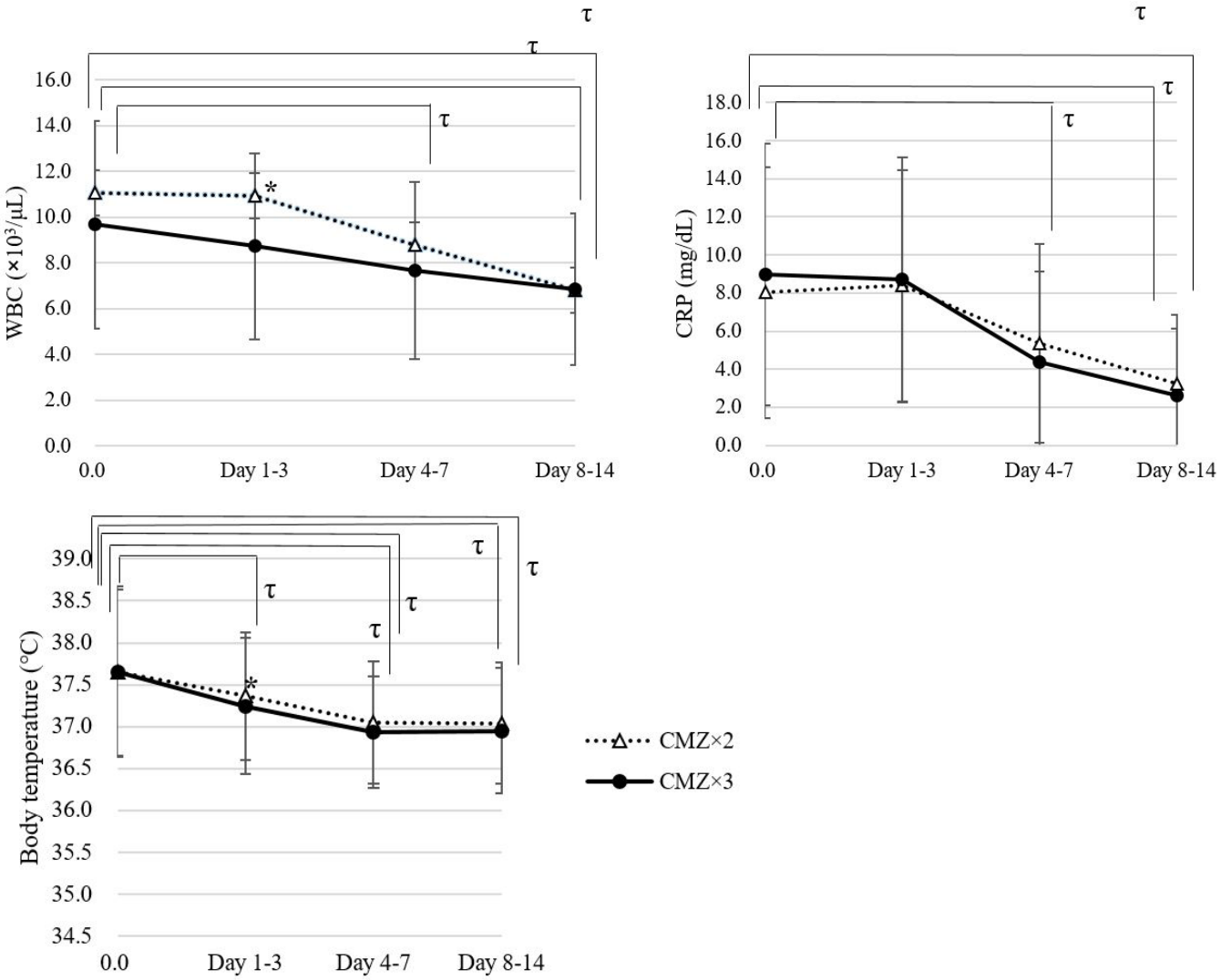
	Regular Dose		**High Dose**		*P* value
	n	**(%)**	**n**	**(%)**	
Overall	12/62	(19.4)	24/81	(29.6)	0.161
a					
T-bil increased	1.7/58	(1.7)	1/78	(1.3)	0.611
b					
Scr increased	1/62	(1.6)	1/81	(1.2)	0.599
b					
AST increased	5/62	(8.1)	12/81	(14.8)	0.329
b					
ALT increased	6/62	(9.7)	18/81	(22.2)	0.047
a					

a; Chi square test for categorical data.

b; Chi square test (yates correction) for categorical data

Table 4: The number of patients of substantially abnormal laboratory values. (n=143)

Changes of inflammation markers: Changes in WBC count, CRP levels, and body temperature were observed for two weeks after initiation of CMZ therapy (Figure 1). The changes in WBC count and body temperature after 1–3 days of initiation of CMZ therapy were observed in the high-dose group, which was significantly lower than that in the regular dose group. Additionally, the levels of each inflammatory marker in the high-dose group showed a decreasing trend after CMZ therapy earlier than those in the regular-dose group. We evaluated the efficacy of CMZ within the same population after classification according to renal function. In the normal renal function group (CLcr ≥ 50), the levels of each inflammatory marker in the high-dose group showed a decreasing trend after CMZ therapy earlier than those of the regular-dose group. In contrast, significant changes related to the decreasing tendency of inflammatory marker levels were not observed in WBC count and CRP levels in patients with abnormal renal function (CLcr < 50) receiving high-dose CMZ treatment.



Data are the mean ± S.D. (standard deviation).

τ: $p < 0.0083$ (nadir vs before administration of cefmetazole (CMZ) ; Bonferroni/dunnett's)

*: $p < 0.05$ (each value at point within two groups; Mann-Whitney's U test)

Regular dose group (CMZ 2g every 12 hour), n=62; High dose group (CMZ 2g every 8 hour), n = 81.

Figure 1: Time-dependent change in body temperature, WBC and CRP of all patients during and after cefmetazole therapy started

The microbiological efficacy: Table 5 showed that eradication rate of patients who bacteria were detected before CMZ administration. Microbiologically efficacious in the high-dose group was higher than that of patients in the regular-dose group (27.5% vs. 33.8%, $p = 0.455$).

	Regular dose		High dose		*P*
	n	(%)	n	(%)	
Microbiologically efficacious	14/51	(27.5)	24/71	(33.8)	0.455

Chi square test for categorical data.

Table 5: The microbiological efficacy

Sub-analysis of patients who received CMZ against bacteremia caused by *E. coli*:

We performed a sub-analysis for the purpose of unifying the conditions of the target patients. CMZ is frequently used for *E. coil* in clinical practice. Therefore, the patients with *E. coli* detected in blood cultures were included in the sub-analysis. *E. coli* was detected in the blood of 70 patients (Table 6). The number of these patients in the regular-dose and high-dose groups was 32 and 38, respectively. All *E. coli* isolates had MIC ≤ 16 mg/L. There was no significant difference in the detection frequency of ESBL-producing *E. coli* between the regular-dose and high-dose groups (31.3% vs. 34.2%, $p = 0.793$). The high-dose group showed significantly higher CLcr rates (37.4 [13.0–106.6] vs. 64.1 [36.0–140.4], $p < 0.001$) as well as higher percentage of patients with CLcr ≥ 50 mL/min (25.0% vs. 76.3%, $p < 0.001$) than the regular-dose group. There was no significant difference in the microbiologically efficacious between the regular-dose and high-dose groups (37.5% vs. 31.6%, $p = 0.603$).

The changes in WBC count, CRP levels, and body temperature observed for two weeks after CMZ therapy initiation in the sub-analysis group are shown in Figure 2. The level of each inflammatory marker showed a decreasing trend. The changes in the values of WBC count and CRP levels observed after 4–7 days of CMZ therapy were significantly lower in the high-dose group than in the regular-dose group. Body temperature showed a decreasing tendency after CMZ therapy earlier in the high-dose group than in the regular-dose group.

	Regular dose (N=32)	**High dose** (N=38)	***P* value**
Age (years)	83.0 (25.0-92.0)	77.5 (37.0-95.0)	0.008 a
Body weight (kg)	51.4 (30.8-80.0)	54.3 (38.8-86.2)	0.128 a
Sex (Male/Female)	14/18	16/22	0.890 b
Used immunosuppressant (%)	21.9 (7/32)	7.9 (3/38)	0.186 c
With diabetes (%)	34.4 (11/32)	31.6 (12/38)	0.804 b
Producing ESBL (%)	31.3 (10/32)	34.2 (13/38)	0.793 b
Duration (days)	7.0 (3.0-55.0)	6.0 (3.0-20.0)	0.777 a
BUN (mg/dL)	19.6 (7.8-70.0)	14.5 (4.9-24.8)	<0.001 a
Scr (mg/dL)	1.1 (0.4-3.4)	0.7 (0.4-1.1)	<0.001 a
CLcr (mL/min)	37.4 (13.0-106.6)	64.1(36.0-140.4)	<0.001 a
CLcr ≥ 50mL/min (%)	25.0 (8/32)	76.3 (29/38)	<0.001 b
Microbiologically efficacious	12/32 (37.5)	12/38 (31.6)	0.603 b

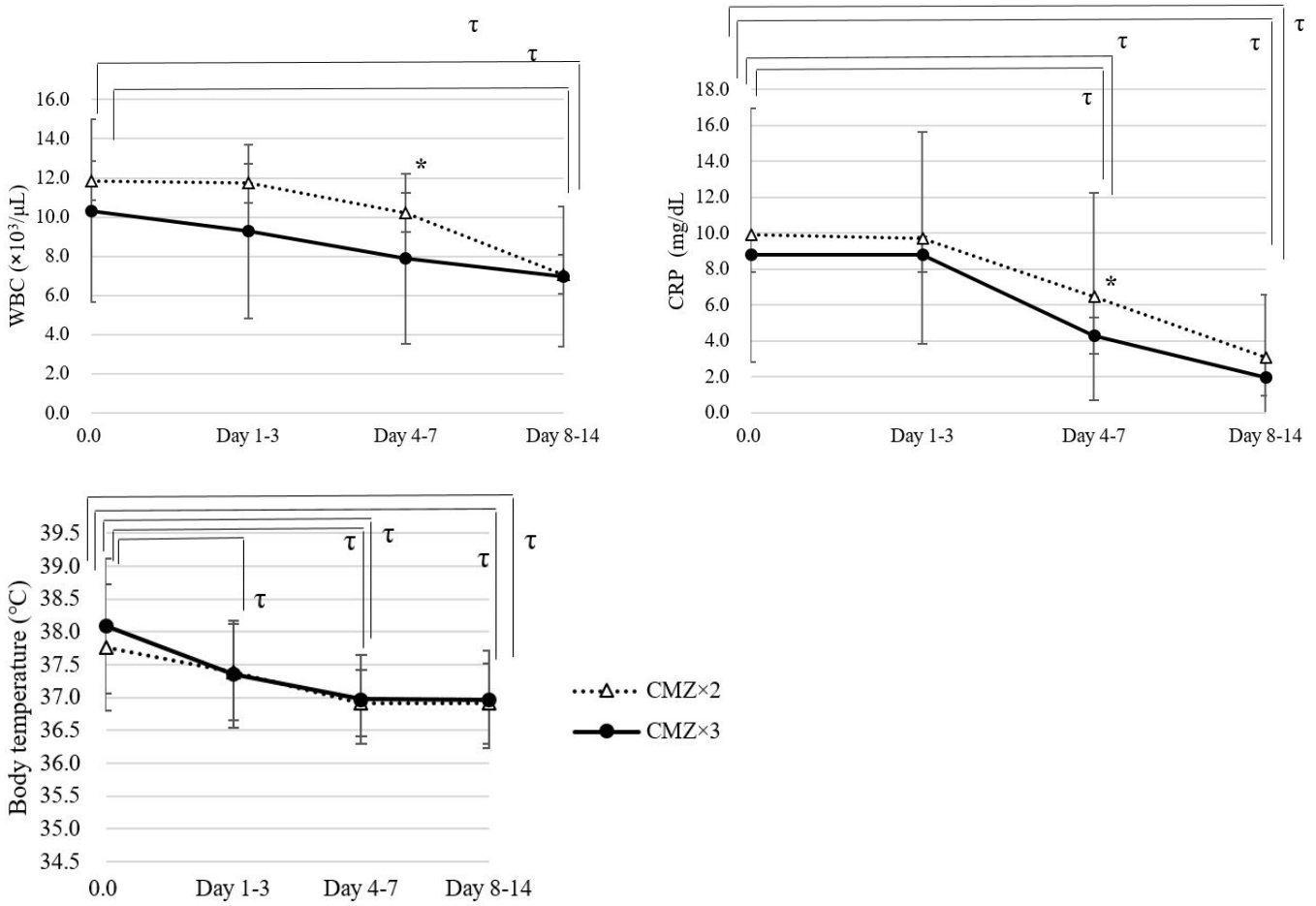
a; Mann-Whitney U test for continuous data. (Median (min-max))

b; Chi square test for categorical data

c; Chi square test (yates correction) for categorical data

ESBL; Extended spectrum β-lactamases

Table 6: Sub-analysis of patients who received cefmetazole against bacteremia caused by *Escherichia colil*



Data are the mean ± S.D. (standard deviation).

τ: $p < 0.0083$ (nadir vs before administration of cefmetazole (CMZ) ; Bonferroni/dunnett's)

*: $p < 0.05$ (each value at point within two groups; Mann-Whitney's U test)

Regular dose group (CMZ 2g every 12 hour), n=32; High dose group (CMZ 2g every 8 hour), n = 38.

Figure 2: Time-dependent change in body temperature, WBC and CRP of patients detected *Escherichia coli* from blood during and after cefmetazole therapy started

Discussion

CMZ has only been used in Japan, and its antibiotic spectrum has some implications in antimicrobial resistance strategy. CMZ, a cephamycin, is stable against hydrolysis by ESBL, and it showed robust in vitro activity with low MIC against ESBL-*Enterobacterales* isolates [25]. Additionally, CMZ can be an alternative to carbapenems for the treatment of infections caused by ESBL-*Enterobacterales* [8]. However, clinical data on the use of CMZ for the treatment of ESBL-*Enterobacterales*-associated infections are limited [8,9,25,26]. Hamada et al. [27] evaluated the efficacy and appropriate dosing regimen of CMZ for invasive urinary tract infections caused by ESBL-producing *E. coli* using estimated plasma % time above MIC and CMZ susceptibility for bacteria identified from patients [28]. They reported that 1 g CMZ infused for over 1 h every 8 h is effective for the treatment of invasive urinary tract infections caused by ESBL-producing *E. coli* with CMZ MIC < 4 mg/L [27]. However, there were some cases treated with high CMZ dose (2g ever 8h) in Aichi Medical University Hospital. The clinical data for the dose over CMZ 2g every 12 h have not been previously validated. Thus, the aim of this study was to evaluate the efficacy and safety of a high-dose CMZ therapy (2 g every 8 h). We used DIC score and qSOFA to evaluate severity. In general, sepsis is suspected in patients with qSOFA score ≥ 2, and DIC derived from septic is suspected in patients with DIC score ≥ 4 [29,30]. However, most of this study patients showed a DIC score < 4 and qSOFA < 2 points. Hence, it seemed that there were few severe cases. Despite the few numbers of severe cases, the high dose CMZ therapy were used for this study patients due to the recommendation by ICT (67.7% vs. 92.6%, $p < 0.001$).

Consequently, the proportion of patients showing at least one abnormal laboratory value was higher in the high-dose group than in the regular-dose group (29.6% vs. 19.4%, $p = 0.161$). Further, ALT levels were significantly elevated only in the high-dose group (22.2% vs. 9.7%, $p = 0.047$). The hepatobiliary disorders related to second-generation cephalosporins have been reported [31]. Regarding effectiveness, there was no significantly difference in the microbiologically efficacy between high-dose group and regular-dose group (27.5% vs. 33.8%, $p = 0.455$). However, patients receiving a high CMZ dose exhibited a significantly lower level of inflammatory markers and showed a decreasing tendency earlier than that of the regular-dose group.

Most components of CMZ are excreted in the urine as unchanged bodies with antibacterial activity. Considering the PK character [32] high dose administration of CMZ in patients with abnormal renal function (CLcr < 50) is expected to elevate blood CMZ concentration and result in increased incidences of abnormal laboratory values.

However, in the present study, patients with abnormal renal function (CLcr < 50) showed the opposite trend compared with patients with normal renal function (CLcr ≥ 50). The proportion of patients with overall substantially abnormal laboratory values was higher in the regular-dose group than in the high-dose group (17.1% vs. 7.1%, $p = 0.656$). Regarding effectiveness, WBC count and CRP levels in the high-dose group did not show a significant decreasing trend after CMZ therapy. We considered two reasons for the tendency of patients with normal renal function to differ from patients with abnormal renal function in terms of efficacy and safety. First, dehydration due to infection might be induced temporarily renal failure, and base renal function was not decreased. Seconds, this might be due to the fact that only 14 patients with abnormal renal function received high CMZ dose, and therefore, appropriate measure of tendency was not observed owing to the limited number of samples.

Furthermore, we performed a sub-analysis to evaluate the efficacy of CMZ therapy in patients who received CMZ treatment against bacteremia caused by *E. coli.* In our sub-analysis, there were no significant differences in the clinical characteristics between the high-dose and regular-dose groups (Table 6). Although all inflammatory markers showed a decreasing trend after CMZ therapy in both regimens, improvement in levels of inflammatory markers in the high-dose group was observed earlier than that in the regular-dose group. Hence, high-dose administration of CMZ (2 g every 8 h) was considered as one of the choices to treat bacteremia caused by *E. coli* with MIC ≤ 16 mg/L.

Several considerations should be made when interpreting our results. First, this was a retrospective study with small sample size, which might have affected the results of significant differences in the clinical efficacy and safety between CMZ treatments. Thus, further investigation in a large population is needed to support the results of safety. Second, we did not measure the blood CMZ concentrations and exact MIC of *E. coli* derived from blood because of the retrospective nature of the study. Therefore, we could not calculated TAM of CMZ against *E. coli.* Finally, we evaluated the clinical effectiveness of CMZ treatment based only on the inflammatory markers and microbiological data. Cinical symptoms were not included in the evaluation of clinical effectiveness.

Conclusion

In conclusion, we revealed that improvement in inflammatory markers after high CMZ dose treatment was observed earlier than that after regular dose treatment, particularly in patients with normal renal function (CLcr > 50). Moreover, treatment with a high CMZ dose (2 g every 8 h) against bacteremia caused by *E. coli* with MIC ≤ 16 mg/L was found to be effective. However, high CMZ dose was associated with a higher risk of abnormal laboratory values than regular-dose treatment and inflammation markers also showed decreasing tendency after regular CMZ treatment. Therefore, we recommended to select the regular CMZ dose (2 g every 12 h) as the patients with general infections and consider to select the high CMZ dose (2 g every 8 h) as the patients with symptoms worsen and normal liver function.

Acknowledgements

The authors thank all clinicians and pharmacists who provided data for this project. We would like to thank Editage (www.editage.com) for English language editing.

Funding

No funding was received for this project.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests

Mikamo H received research funding from Sumitomo Dainippon Pharma Co., Ltd., Taisho Toyama Pharmaceutical Co. Ltd., Daiichi Sankyo Co., Ltd., Pfizer Co. Ltd., Astellas Pharma Inc., MSD K.K., Toyama Chemical Co. Ltd., MIYARISAN Pharmaceutical Co., Ltd., Shionogi & Co. Ltd.; Consulting fee/honorarium from Sumitomo Dainippon Pharma Co., Ltd., Taisho Toyama Pharmaceutical Co. Ltd., Daiichi Sankyo Co., Ltd., Pfizer Co. Ltd., MSD K.K., Astellas Pharma Inc., MIYARISAN Pharmaceutical Co., Ltd.

References

1. Horie A, Nariai A, Katou F, Abe Y, Saito Y, et al. (2019) Increased community-acquired upper urinary tract infections caused by extended-spectrum beta-lactamase-producing Escherichia coli in children and the efficacy of flomoxef and cefmetazole. Clin Exp Nephrol 23: 1306-14.

2. Vardakas KZ, Tansarli GS, Rafailidis PI, Falagas ME (2012) Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum beta-lactamases: a systematic review and meta-analysis. J Antimicrob Chemother 67: 2793-803.

3. R Cofsky, K Vangala, R Haag, R Recco, E Maccario, et al. (2022) The cost of antibiotic resistance: effect of resistance among Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudmonas aeruginosa on length of hospital stay. Infect Control Hosp Epidemiol 23: 106-8.

4. Schwaber MJ, Carmeli Y (2007) Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. J Antimicrob Chemother 60: 913-20.

5. Leistner R, Gurntke S, Sakellariou C, Denkel LA, Bloch A, et al. (2014) Bloodstream infection due to extended-spectrum beta-lactamase (ESBL)-positive K. pneumoniae and E. coli: an analysis of the disease burden in a large cohort. Infection 42: 991-7.

6. Ramphal R, Ambrose PG (2006) Extended-spectrum beta-lactamases and clinical outcomes: current data. Clin Infect Dis 42 Suppl 4: S164-72.

7. Paterson DL, Ko WC, Von Gottberg A, Mohapatra S, Casellas JM, et al. (2004) Antibiotic therapy for Klebsiella pneumoniae bacteremia: implications of production of extended-spectrum beta-lactamases. Clin Infect Dis 39: 31-7.

8. Fukuchi T, Iwata K, Kobayashi S, Nakamura T, Ohji G (2016) Cefmetazole for bacteremia caused by ESBL-producing enterobacteriaceae comparing with carbapenems. BMC Infect Dis 16: 427.

9. Matsumura Y, Yamamoto M, Nagao M, Komori T, Fujita N, et al. (2015) Multicenter retrospective study of cefmetazole and flomoxef for treatment of extended-spectrum-beta-lactamase-producing Escherichia coli bacteremia. Antimicrob Agents Chemother 59: 5107-13.

10. Muhammed M, Flokas ME, Detsis M, Alevizakos M, Mylonakis (2017) Comparison Between Carbapenems and beta-Lactam/beta-Lactamase Inhibitors in the Treatment for Bloodstream Infections Caused by Extended-Spectrum beta-Lactamase-Producing Enterobacteriaceae: A Systematic Review and Meta-Analysis. Open Forum Infect Dis 4: ofx099.

11. Kobayashi H, Kitamoto O, Saito A, Kato Y, Tomizawa M, et al. (1983) Comparative clinical study of cefpiramide (SM-1652) and cefmetazole for the treatment of respiratory tract infections by a double-blind method. Kansenshogaku Zasshi 57: 587-629.

12. Ishigami J, Kamidono S, Arakawa S, Kataoka N, Nakano K, et al. (1983) Double-blind comparative clinical study of cefpiramide (SM-1652) and cefmetazole in complicated urinary tract infections. Kansenshogaku Zasshi 57: 695-723.

13. Craig WA (2003) Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect Dis Clin North Am 17: 479-501.

14. Wataru T, Sho T, Marina H, Yuki I, Xiaoxi L, et al. (2021) Cefmetazole as an Alternative to Carbapenems Against Extended-Spectrum Beta-Lactamase-Producing Escherichia coli Infections Based on In Vitro and In Vivo Pharmacokinetics/Pharmacodynamics Experiments. Pharm Res 38: 1839-46.

15. Wu CC, Tai CH, Liao WY, Wang CC, Kuo CH, et al. (2019) Augmented renal clearance is associated with inadequate antibiotic pharmacokinetic/pharmacodynamic target in Asian ICU population: a prospective observational study. Infect Drug Resist 12: 2531-41.

16. Ehmann L, Zoller M, Minichmayr IK, Scharf C, Maier B, et al. (2017) Role of renal function in risk assessment of target non-attainment after standard dosing of meropenem in critically ill patients: a prospective observational study. Crit Care 21: 263.

17. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, et al. (2014) DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 58: 1072-83.

18. Blot SI, Pea F, Lipman J (2014) The effect of pathophysiology on pharmacokinetics in the critically ill patient--concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev 77: 3-11.

19. Masich AM, Heavner MS, Gonzales JP, Claeys KC (2018) Pharmacokinetic/Pharmacodynamic Considerations of Beta-Lactam Antibiotics in Adult Critically Ill Patients. Curr Infect Dis Rep 20: 9.

20. Delattre IK, Taccone FS, Jacobs F, Hites M, Dugernier T, et al. (2017) Optimizing beta-lactams treatment in critically-ill patients using pharmacokinetics/pharmacodynamics targets: are first conventional doses effective? Expert Rev Anti Infect Ther 15: 677-88.

21. Sjovall F, Alobaid AS, Wallis SC, Perner A, Lipman J, et al. (2018) Maximally effective dosing regimens of meropenem in patients with septic shock. J Antimicrob Chemother 73: 191-8.

22. Burger R, Guidi M, Calpini V, Lamoth F, Decosterd L, et al. (2018) Effect of renal clearance and continuous renal replacement therapy on appropriateness of recommended meropenem dosing regimens in critically ill patients with susceptible life-threatening infections. J Antimicrob Chemother 73: 3413-22.

23. Kato H, Hamada Y, Hagihara M, Hirai J, Nishiyama N, et al. (2016) Retrospective study of teicoplanin loading regimen that rapidly achieves target 15-30 μg/mL serum trough concentration. J Infect Chemother 22: 308-13.

24. Cockcroft D, Gault Mv (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31-41.

25. Doi A, Shimada T, Harada S, Iwata K, Kamiya T (2013) The efficacy of cefmetazole against pyelonephritis caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae. Int J Infect Dis 17: 159-63.

26. Mawatari M, Hayakawa K, Fujiya Y, Yamamoto K, Kutsuna S, et al. (2017) Bacteraemic urinary tract infections in a tertiary hospital in Japan: the epidemiology of community-acquired infections and the role of non-carbapenem therapy. BMC Res Notes 10: 336.

27. Hamada Y, Matsumura Y, Nagashima M, Akazawa T, Doi Y, et al. (2021) Retrospective evaluation of appropriate dosing of cefmetazole for invasive urinary tract infection due to extended-spectrum beta-lactamase-producing Escherichia coli. J Infect Chemother 27: 1602-6.

28. Tomizawa A, Nakamura T, Komatsu T, Inano H, Kondo R, et al (2017) Optimal dosage of cefmetazole for intraoperative antimicrobial prophylaxis in patients undergoing surgery for colorectal cancer. J Pharm Health Care Sci 3: 1.

29. Singer M, Deutschman C, Christopher S, Shankar M, Annane D, et al. (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315: 801-10.

30. Dhainaut J, Yan S, Joyce D, Pettilä V, Basson B, et al. (2004) Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. J Thromb Haemost 2:1924-33.

31. Sipos M, Farcas A, Leucuta DC, Bucsa C, Huruba M, et al. (2021) Second-Generation Cephalosporins-Associated Drug-Induced Liver Disease: A Study in VigiBase with a Focus on the Elderly. Pharmaceuticals (Basel) 14: 441.

32. Kawada Y (1979) Profile of cefmetazole. II. Absorption, excretion, distribution and metabolism (author's transl). Kansenshogaku Zasshi 53: 66-74.