Effectiveness and Safety of Generic Formulation of Cefoperazone/Sulbactam (Bacticep®) in Treatment of Infections at Siriraj Hospital

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Objective: *To compare the effectiveness and safety of generic cefoperazone/sulbactam (Bacticep®) and original cefoperazone/sulbactam (Sulperazon®) in treatment of infections in hospitalized patients at Siriraj Hospital.*
Material and Method: *Hospitalized patients aged 18 years and older who received cefoperazone/sulbactam for at least 48 hours were identified from the Siriraj Hospital pharmacy database. Medical records of identified patients were reviewed and relevant information was extracted and transferred onto pre-printed case record forms. Patient data relating to demographics, clinical features of infections, antibiotic therapy, and treatment outcomes were evaluated and compared between patients who received generic and original cefoperazone/sulbactam.*
Results: *Two hundred twenty nine hospitalized patients who had infections and received original or generic cefoperazone/sulbactam were included. Baseline characteristics and clinical features of infections in both groups were comparable. Favorable outcomes (72.9% vs. 72.2%, p = 1.00) and infection-related deaths (4.7% vs. 11.1%, p = 0.16) between generic cefoperazone/sulbactam group and original cefoperazone/sulbactam group, respectively, were not significantly different. Generic cefoperazone/sulbactam favorable outcomes were found to be non-inferior to original cefoperazone/sulbactam (p = 0.04), with lower bound of one-sided 95% CI for difference in favorable outcome within the pre-specified non-inferiority margin of -10% (95% CI: 0.7% with lower bound of -9.3). No significant differences in adverse events were observed between groups.*
Conclusion: *Generic cefoperazone/sulbactam (Bacticep®) was found to be non-inferior to original cefoperazone/sulbactam for therapy of infections in hospitalized patients at Siriraj Hospital.*

Keywords: *Cefoperazone/sulbactam, Effectiveness, generic, Non-inferiority, Original, Safety*

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A key factor when prescribing drugs is the cost of the drug. Generic formulation of any particular drugs is usually much cheaper than the original formulation. Many generic formulations of parenteral antimicrobial agents are life-saving drugs, which need to be safe and effective in treatment of severe and life threatening infections. However, registration of generic formulations of parenteral drugs with Thai Food and Drug Administration do not need any data regarding bioequivalence and therapeutic equivalence of generic drug when compared with the original drug. As a result, many physicians are reluctant to use generic formulations of life-saving drugs in clinical practice. Although many generic formulations of parenteral antimicrobial agents were observed to be non-inferior to their original formulations[1-3], some generic formulations of parenteral antimicrobial agents were found to be inferior to their original formulations[4,5]. Therefore, it may be necessary to determine the therapeutic equivalence of generic formulations of parenteral antimicrobial agents that are used to treat severe and life-threatening infections.

Cefoperazone/sulbactam is a beta-lactam antibiotic combined with a beta-lactamase inhibitor that has demonstrated activity against gram-positive, gram-negative, and anaerobic bacteria, including *Pseudomonas aeruginosa,* and *Acinetobacter baumannii*[6-8]. Cefoperazone/sulbactam has been used to treat several nosocomial infections, including nosocomial pneumonia, intra-abdominal infections, sepsis, and infections in febrile neutropenic patients[9]. Adverse effects of cefoperazone/sulbactam are mild and infrequent. Patients who receive cefoperazone/

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sulbactam may experience mild dizziness, nausea, and/or vomiting. Cefoperazone may cause abnormal bleeding by inhibiting vitamin K epoxide reductase. Accordingly, it should be used with caution in patients at increased risk of bleeding. Generic cefoperazone/sulbactam (Bacticep®) is available at Siriraj Hospital since October 2009.

The present study aimed to compare the effectiveness and safety of generic cefoperazone/sulbactam (Bacticep®) with the original product for treatment of infections in hospitalized patients at Siriraj Hospital.

Material and Method

Hospitalized patients aged 18 years and older who received cefoperazone/sulbactam for at least 48 hours were identified from the Siriraj Hospital pharmacy database. Data from patients who received cefoperazone/sulbactam, both original and generic, between October 2008 and July 2014 were collected. Patient medical records were reviewed for demographic data, underlying conditions, co-morbidities, indication for prescribing cefoperazone/sulbactam, type and site of infections, causative pathogenic organisms, previous and concomitant antibiotics, microbiological and clinical outcomes, and adverse events. The objective of this study was to demonstrate non-inferiority of generic cefoperazone/sulbactam (Bacticep®) relative to original cefoperazone/sulbactam in terms of overall favorable outcome, cure, and improvement at the end of treatment. Generic cefoperazone:sulbactam was prepared in ratio of 1:1 while cefoperazone:sulbactam was prepared in ratio of 1:0.5, however, we compared exactly dosage of cefoperazone and sulbactam between groups.

The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB). Sample size was calculated based on testing for non-inferiority test with a power of 80% and a one-sided significance level of 5%. It was assumed that overall favorable outcomes with the original drug were 70% and non-inferiority margin for the generic drug was 10%. Using nQuery Advisor 5.0 (Statistical Solutions, Clearwater, FL, USA), a sample size of at least 260 patients per group was calculated for purposes of demonstrating non-inferiority of generic cefoperazone/sulbactam.

Collected data were managed and analyzed using PASW Statistics 18.0 (SPSS, Inc., Chicago, IL, USA) and R software version 3.1.2 (R Development Core Team, 2015; Vienna, Austria). Continuous variables were expressed as mean ± standard deviation or median and range, with categorical variables presented as frequency and percentage. Unpaired t-test or Mann-Whitney U test was used to compare continuous variables between groups. Categorical variables were compared using Chi-square test or Fisher's exact test. A multiple logistic regression analysis was used to identify factors independently associated with clinical outcome. All variables with $p<0.10$ in univariate analysis were included in multivariate analysis. Non-inferiority test was used to compare favorable outcome between generic formulation and original cefoperazone/sulbactam. One-sided 95% confidence interval (95% CI) of the difference in favorable outcome between groups was also computed. Two-sided or one-sided test, as appropriate, was used for all comparisons and a p-value of 0.05 or less was considered to be statistically significant.

Results

Medical records of 950 patients who received cefoperazone/sulbactam were reviewed. Only 229 patients (85 patients in the generic cefoperazone/sulbactam group and 144 patients in the original cefoperazone/sulbactam group) met eligibility criteria and had sufficient information for us to determine outcome of treatment. Many excluded patients received cefoperazone/sulbactam for surgical prophylaxis or received cefoperazone/sulbactam for only several days before switching to other antibiotics; cases for which therapeutic outcome could not be assessed. Characteristics of patients in both groups are shown in Table 1.

There were no significant differences in age, gender, body weight, and serum creatinine levels between the generic and original drug groups. Most of the patients (85.6%) had co-morbidities. Respiratory tract infection was the most common site of infection and *A. baumannii* followed by *P. aeruginosa* were the most common causative pathogenic organisms as shown in Table 2. Hematologic malignancy and hypertension were more common in patients who received generic cefoperazone/sulbactam, with cancer being more common in those who received original cefoperazone/sulbactam. Prior use of antibiotics before receiving cefoperazone/sulbactam was similar in both groups. There was no report of adverse event relating to cefoperazone/sulbactam in either the generic or original drug groups. Average dosage and duration of cefoperazone/sulbactam between groups were significantly different, as shown in Table 3. Average dose of cefoperazone/sulbactam was higher in the

Table 1. Patient characteristics

	Generic cefoperazone/sulbactam (n = 85)	Original cefoperazone/sulbactam (n = 144)	*p*-value
Age (year)			0.18
Mean ± SD	62.2±16.2	64.4±20.1	
Median (min, max)	65 (21, 89)	70.5 (18, 102)	
Gender			0.80
Male	42 (49.4)	75 (52.1)	
Female	43 (50.6)	69 (47.9)	
Body weight (kg)			0.81
Mean ± SD	52.0±6.0	51.2±7.1	
Creatinine (mg/dL)			0.54
Mean ± SD	1.2±1.1	2.1±3.3	
Median (min, max)	0.9 (0.2, 7.1)	0.9 (0.3, 22)	
Department			0.22
Medicine	38 (45.2)	55 (39.9)	
Surgery	43 (51.2)	73 (52.9)	
Other	4 (4.7)	16 (11.1)	
Underlying disease	79 (92.9)	117 (81.3)	0.03
Diabetes mellitus	27 (31.8)	34 (23.6)	0.23
Heart disease	17 (20.0)	27 (18.8)	0.95
Hematologic malignancy	20 (23.5)	12 (8.3)	0.003
Renal disease	21 (24.7)	18 (12.5)	0.03
Cancer	1 (1.2)	10 (6.9)	0.06
Pulmonary disease	3 (3.5)	11 (7.6)	0.33
Liver disease	3 (3.5)	2 (1.4)	0.36
HIV infection	0 (0)	2 (1.4)	0.53
Hypertension	39 (45.9)	24 (16.7)	<0.001
Others	41 (48.2)	67 (46.5)	0.91
Previous use of antibiotic	51 (60.0)	73 (50.7)	0.22

Data presented as n (%), unless otherwise specified

generic drug group than in the original drug group. Average duration of cefoperazone/sulbactam was shorter in the generic drug group than in the original drug group. Outcomes of cefoperazone/sulbactam treatment are shown in Table 4.

There were no significant differences between generic cefoperazone/sulbactam group and original cefoperazone/sulbactam group regarding favorable outcomes, infection-related death, and overall mortality. Non-inferiority analysis of favorable outcomes for both groups is shown in Table 5. Generic cefoperazone/sulbactam was found to be non-inferior to original cefoperazone/sulbactam regarding overall favorable outcomes ($p = 0.04$), with lower bound of one-sided 95% CI for difference in favorable outcome within the pre-specified non-inferiority margin of -10% (95% CI: 0.7% with lower bound of -9.3). Length of cefoperazone/sulbactam treatment was significantly associated with favorable outcome in all patients (OR: 0.85, 95% CI: 0.79-0.92; $p<0.001$). Multivariate analysis revealed duration of cefoperazone/sulbactam treatment and respiratory tract infection to be significantly associated with clinical outcome. However, comorbidities, dosage of cefoperazone/sulbactam, and type of cefoperazone/sulbactam formulation were not significantly associated with clinical outcome.

Discussion

The present study was unable to enroll the calculated minimum number of sample size participants for this study. In addition to patients who did not meet the eligibility criteria and patients for whom there was inadequate information to determine outcome, many of the 950 patients who received cefoperazone/sulbactam were switched to other antibiotics due to being infected with bacteria that were not susceptible to cefoperazone/sulbactam or they did not improve after receiving cefoperazone/sulbactam for several days over the past few years. Several underlying conditions and average dose per day of cefoperazone/sulbactam were significantly different

Table 2. Infections in the patients receiving cefoperazone/sulbactam

	Generic cefoperazone/sulbactam (n = 85)	Original cefoperazone/sulbactam (n = 144)	*p*-value
Site of infection			
Respiratory	41 (42.8)	88 (61.1)	0.08
Urinary tract	13 (15.3)	8 (5.6)	0.03
Skin and soft tissue	6 (7.1)	13 (9.0)	0.78
CRBSI	1 (1.2)	2 (1.4)	1.00
Intra-abdominal	8 (9.4)	5 (3.5)	0.08
Central nervous system	2 (2.4)	1 (0.7)	0.64
Bone and joint	0 (0)	1 (0.7)	1.00
Primary bacteremia	2 (2.4)	9 (6.3)	0.22
Causative organism			
E. coli	6 (7.1)	2 (1.4)	0.05
ESBL *E. coli*	4 (4.7)	7 (4.9)	1.00
K. pneumoniae	6 (7.1)	13 (9.0)	0.78
ESBL *K. pneumoniae*	9 (10.6)	10 (6.9)	0.47
P. aeruginosa	13 (15.3)	23 (16.0)	1.00
A. baumannii	32 (37.6)	57 (39.6)	0.88
Unspecified gram-negative rod	9 (10.6)	13 (9.0)	0.88
MSSA	3 (3.5)	3 (2.1)	0.67
MRSA	5 (5.9)	10 (6.9)	0.97
Enterococcus	5 (5.9)	2 (1.4)	0.11
Coagulase-negative staphylococci	1 (1.2)	2 (1.4)	1.00
Unspecified gram-positive cocci	1 (1.2)	1 (0.7)	1.00
Unknown	23 (27.1)	39 (27.1)	1.00

CRBSI = catheter-related bloodstream infection; ESBL = extended-spectrum beta-lactamases; MSSA = methicillin-sensitive *S. aureus*; MRSA = methicillin-resistant *S. aureus*
Data presented as n (%)

Table 3. Dosage and duration of cefoperazone/sulbactam

	All patients (n = 229)	Generic cefoperazone/sulbactam (n = 85)	Original cefoperazone/sulbactam (n = 144)	*p*-value
Dosage (g/day)				
Mean ± SD	4.1±1.6	4.7±1.9	3.7±1.4	<0.001
Median (min, max)	4 (1, 9)	4.5 (2, 9)	3 (1, 9)	
Duration (day)				
Mean ± SD	10.0±6.0	9.1±5.9	10.5±6.0	0.03
Median (min, max)	9 (2, 49)	7 (3, 49)	9 (2, 38)	

between the generic cefoperazone/sulbactam group and the original cefoperazone/sulbactam group. This may be explained by the fact that most of the patients in both groups received cefoperazone/sulbactam at different periods within the study timeframe.

Patients who received original cefoperazone/sulbactam were hospitalized and received original cefoperazone/sulbactam prior to the availability of generic cefoperazone/sulbactam. Original cefoperazone/sulbactam was rarely used after generic cefoperazone/sulbactam became available at Siriraj Hospital in October 2009. By the time generic cefoperazone/sulbactam became available, it is plausible that more patients may have been infected with cefoperazone/sulbactam-resistant bacteria, which may have required higher doses of generic cefoperazone/sulbactam[10,11]. Such differences should not affect outcomes of cefoperazone/sulbactam treatment, because comorbidities of enrolled patients and average dose per day of generic cefoperazone/sulbactam were found not to be associated with clinical outcomes, according to multivariate analysis.

Average duration of cefoperazone/sulbactam treatment was different between the original cefoperazone/sulbactam group and the generic cefoperazone/sulbactam group and duration of cefoperazone/sulbactam treatment was found to associate with clinical outcome in these 229 patients.

Table 4. Outcomes of cefoperazone/sulbactam treatment

	Generic cefoperazone/sulbactam (n = 85)	Original cefoperazone/sulbactam (n = 144)	*p*-value
Clinical outcomes			
Favorable outcomes (cure or improve)	62 (72.9)	104 (72.2)	0.97
Infection stable	2 (2.3)	5 (3.5)	1.00
Infection worse	17 (20.0)	19 (13.2)	0.24
Died of infection (while being treated with cefoperazone/sulbactam)	4 (4.7)	16 (11.1)	0.16
Discharge status			
Alive	64 (77.1)	93 (64.6)	0.12
Died of infection	13 (15.7)	35 (24.3)	0.15
Died of other causes	5 (6.0)	14 (9.7)	0.44
Against advice	1 (1.2)	0 (0)	0.37
Others*	2 (2.3)	2 (1.4)	0.63
Overall mortality	18 (21.2)	48 (33.3)	0.07

Data presented as n (%)
* Others: refer to other hospital, not related to infection

Table 5. Favorable outcomes of cefoperazone/sulbactam treatment

	Generic cefoperazone/ sulbactam (n = 85)	Original cefoperazone/ sulbactam (n = 144)	Difference (one-sided 95% CI)	Non-inferiority test (*p*-value)
Favorable outcomes (cure or improve)	62 (72.9)	104 (72.2)	0.7% (-9.3, ∞)*	0.044**

Data presented as n (%), unless otherwise specified
* Non-inferiority was shown: lower bound of the one-sided 95% CI for difference of favorable outcome between generic cefoperazone/ sulbactam and original cefoperazone/sulbactam was within pre-specified non-inferiority margin of -10%
** Non-inferiority was shown: *p*-value of non-inferiority test was less than significance level of 0.05

This may have resulted from the fact that patients who died while receiving cefoperazone/sulbactam usually had shorter duration of cefoperazone/sulbactam treatment than the patients who survived. Another factor potentially associating with duration and outcome is the fact that patients who did not respond to cefoperazone/sulbactam after receiving cefoperazone/sulbactam for several days usually received other antibiotics, which would have resulted in shorter duration of cefoperazone/sulbactam when compared to patients who responded to cefoperazone/ sulbactam. Respiratory tract infection was associated to unfavorable outcome that may have resulted from it was most common site of infection in hospitalized critically ill patients. There was no evidence that favorable outcome and mortality of patients who received generic cefoperazone/sulbactam (Bacticep®) were inferior to favorable outcome and mortality of patients who received original cefoperazone/ sulbactam (Sulperazon®), based on interim analysis of 229 enrolled patients. Generic cefoperazone/sulbactam (Bacticep®) is one of the parenteral antibiotics, in addition to some generic formulations of meropenem and piperacillin/tazobactam, that were found to be non-inferior to their original formulations[1-3]. It should be noted that the results of the present study could not be generalized regarding the effectiveness and safety of other generic cefoperazone/sulbactam formulations.

What is already known on this topic?

It is known that original cefoperazone/ sulbactam (sulperazon) could treat hospital acquired gram-negative infection thus generic cefoperazone/ sulbactam (bacticep) should have the same treatment efficacy as the original agent.

What this study adds?

The present study found that generic cefoperazone/sulbactam (bacticep) was non-inferior when compared to original agent (sulperazon) for the treatment of infection. This finding was a requirment for using generic agent in Siriraj Hospital.

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Potential conflicts of interest

The authors hereby declare that this study was funded by M&H Manufacturing (Thailand). However, M&H Manufacturing personnel were not involved in any part of the study.

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ประสิทธิผลและความปลอดภัยของยาสามัญ cefoperazone/sulbactam (Bacticep®) ในการรักษาผู้ป่วยโรคติดเชื้อที่โรงพยาบาลศิริราช

พรพรรณ กู้มานะชัย, ศศิมา ทองสาย, วิษณุ ธรรมลิขิตกุล

วัตถุประสงค์: *เพื่อทราบประสิทธิผลและความปลอดภัยของยาสามัญ cefoperazone/sulbactam (Bacticep®) เมื่อเทียบกับยาต้นแบบ (Sulperazon®) ในการรักษาผู้ป่วยโรคติดเชื้อที่โรงพยาบาลศิริราช*

วัสดุและวิธีการ: *ศึกษาผู้ป่วยอายุตั้งแต่ 18 ปีขึ้นไป ที่รับไว้รักษาในโรงพยาบาลศิริราช และได้รับการรักษาด้วยยา cefoperazon/sulbactam ไม่น้อยกว่า 48 ชั่วโมง ที่ได้จากฐานข้อมูลยาของโรงพยาบาลศิริราช โดยเก็บข้อมูลจากเวชระเบียนผู้ป่วย ได้แก่ ข้อมูลพื้นฐาน ลักษณะทางคลินิกของการติดเชื้อ การรักษาด้วยยาต้านจุลชีพ และผลการรักษาของผู้ป่วยที่ได้รับยาสามัญและยาต้นแบบ cefoperazone/sulbactam แล้วนำข้อมูลมาเปรียบเทียบกัน*

ผลการศึกษา: *ผู้ป่วย 229 ราย มีการติดเชื้อและได้รับการรักษาด้วยยา cefoperazone/sulbactam ที่สามารถนำข้อมูลมาวิเคราะห์ได้ ข้อมูลพื้นฐานและลักษณะทางคลินิกของผู้ป่วยทั้งสองกลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ ผลการตอบสนองต่อรักษาของผู้ป่วยกลุ่มยาสามัญและยาต้นแบบ คือ ร้อยละ 72.9 และ 72.2 (p 1.00) ตามลำดับ ส่วนอัตราตายจากการติดเชื้อของผู้ป่วยกลุ่มยาสามัญและยาต้นแบบก็ไม่แตกต่างอย่างมีนัยสำคัญ คือ ร้อยละ 4.7 และ 11.1 (p 0.16) ตามลำดับ ไม่พบความแตกต่างของผลข้างเคียงจากยา*

สรุป: *ยาสามัญ cefoperazone/sulbactam (Bacticep®) มีประสิทธิผลในการรักษาผู้ป่วยโรคติดเชื้อที่โรงพยาบาลศิริราชไม่ด้อยกว่ายาต้นแบบและไม่พบผลข้างเคียงรุนแรงแตกต่างจากยาต้นแบบ*