Cefoperazone/Sulbactam + Co-trimoxazole *vs* Ceftazidime + Co-trimoxazole in the Treatment of Severe Melioidosis: A Randomized, Double-Blind, Controlled Study

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Abstract

A prospective randomized, double-blind, controlled study of cefoperazone/sulbactam (cefoperazone 25 mg/kg/day) + co-trimoxazole (trimethoprim 8 mg/kg/day) *vs* ceftazidime (100 mg/kg/day) + co-trimoxazole (trimethoprim 8 mg/kg/day) in the treatment of severe melioidosis was conducted at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand, from July 1995 to September 1996. A total of 84 patients were enrolled in the study. Forty of them (48%) had culture-proven melioidosis and were randomly assigned to one of the two treatment groups, each group with 20 patients. Two cases (one in each treatment group) were excluded from the final analysis due to incomplete data. There was no significant difference in the mortality rate between the two groups - 16 per cent (3/19) in the cefoperazone/sulbactam group *vs* 21 per cent (4/19) in the ceftazidime group ($p>0.05$). Bacteriological responses of successfully treated patients were similar in both groups, and both treatment regimens were well tolerated.

Cefoperazone/sulbactam + co-trimoxazole can therefore be used as an alternative treatment for severe melioidosis. However, to further support this conclusion, a study with a larger patient population is needed.

Melioidosis is an infection caused by gram-negative bacilli, *Burkholderia pseudomallei*. It is highly endemic in Asia, particularly Southeast Asia and Northern Australia. Because of its diverse clinical presentations, a definite diagnosis is often difficult[1]. Melioidosis is a major cause of community-acquired septicemia (20%) in Northeastern Thailand[2] and its disseminated septicemic form produces a particularly high mortality rate (68-90%)[1,3,4]. Because its clinical course is rapid

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and severe[1], a prompt and accurate diagnosis and treatment with appropriate antibiotics can decrease morbidity and mortality rates.

Ceftazidime, with or without co-trimoxazole, has been used as the standard treatment for severe melioidosis, and mortality rates have dropped[4,5]. Unfortunately, cases of ceftazidime-resistant organisms during treatment have been reported[6] and the cause of this resistance has been ascribed to the mechanism of ß-lactam resistance by ß-lactamase enzyme production[6,7]. When ß-lactamase inhibitors (clavulanate or sulbactam) were added to ß-lactam antibiotics (amoxicillin, ticarcillin, or ampicillin), the minimal inhibitory concentration (MIC) dropped from between twofold to > 64-fold[7].

Cefoperazone has its own activity against *B. pseudomallei* with an MIC of 4 to 32 µg/ml[8,9]. By adding sulbactam to cefoperazone, synergism is expected. In our *in vitro* study (unpublished data), using disk diffusion tests, all 100 strains of *B. pseudomallei* were found to be susceptible to cefoperazone/sulbactam and the MIC90 was only 3 µg/ml. Therefore, cefoperazone/sulbactam might be effective in the treatment of severe melioidosis.

We report the results of a study comparing the clinical outcome and safety of cefoperazone/sulbactam + co-trimoxazole compared with ceftazidime + co-trimoxazole in the treatment of severe melioidosis.

MATERIAL AND METHOD

We conducted a prospective, randomized, double-blind, controlled study from July 1995 to September 1996. We enrolled patients admitted to Srinagarind Hospital (a tertiary care hospital in Northeastern Thailand) with clinical sepsis and who were suspected of having melioidosis. The study protocol was approved by the Research Committee of the Faculty of Medicine, Khon Kaen University, Thailand.

Patient Selection

All adult (aged 14 or older) patients with clinical sepsis which might be due to melioidosis were enrolled by their physicians and randomly assigned to receive either cefoperazone/sulbactam or ceftazidime. Diagnosis of sepsis[10] were based on the presence of two or more of the following signs: 1) body temperature >38°C or < 36°C; 2) tachycardia (> 90 beats per minute); 3) tachypnea (respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mmHg); 4) white blood cell count (WBC) > 12,000 cells/mm^3 or < 4,000 cells/mm^3 or band form > 10%; 5) organ dysfunction indicated by oliguria, mental state change, and lactic acidosis; and 6) hypotension (systolic blood pressure < 90 mmHg or reduction > 40 mmHg from baseline).

Suspected melioidosis was diagnosed based on one of the following five findings: 1) gram-negative bipolar staining or no other definite organism; 2) presence of underlying disease of diabetes, renal insufficiency, or renal stone; 3) signs of dissemination such as skin pustules and blood-borne pneumonia; 4) special organ involvement such as splenic abscess; or 5) rapidly progressive community-acquired pneumonia.

Patients were excluded if they were allergic to ß-lactam antibiotics, terminally ill (likely to die within 24 hours), pregnant, had received anti-melioidotic antibiotics for more than three days, were known to be seropositive to HIV antibodies, had signs of meningitis, or had a negative culture for *B. pseudomallei*.

Treatment

Patients enrolled in the trial were randomly assigned to receive either intravenous infusion of cefoperazone/sulbactam [1:1] [Sulperazon (Pfizer)] (cefoperazone 25 mg/kg/day or 3 g/day of cefoperazone/sulbactam [1:1] in 3 divided doses + co-trimoxazole (trimethoprim 8 mg/kg/day, 6 ampoules/day) over 30 minutes in 3 divided doses); or ceftazidime [Fortum (Glaxo)] 100 mg/kg/day (6 g/day) in 3 divided doses + co-trimoxazole in the same doses as above. The dosage was reduced to ceftazidime 4 g/day or cefoperazone/sulbactam 2 g/day with co-trimoxazole 4 ampoules/day, given in divided doses every 12 hours, if creatinine clearance was less than 20 ml/minute. Vitamin K1 was given intravenously on days 1 and 7 to prevent bleeding due to cefoperazone.

Decisions regarding the use of intravenous fluids, cardiovascular and respiratory support, and surgical intervention were made by attending physicians based on the patient's clinical status. They were not in any way influenced by the study protocol. If the culture was positive for other organisms, the attending physician would adjust the antibiotic based on the organisms and sensitivity results. These patients would be excluded from the study.

Evaluation of the patients

Patients were followed until discharge or death. Blood samples were obtained for culture on day 0 (enrollment date), at 24 and 48 hours, and on day 6. Samples of all other suspected foci of infection were also obtained for culture during admission. Routine hematologic and clinical chemistry tests were done prior to treatment. Vital signs and clinical evaluations were recorded daily during admission.

The primary clinical outcome was the mortality rate at discharge. The secondary outcome was the bacterial clearance from the blood of patients who had an initial positive hemoculture at 24 hours, 48 hours, and on day 6.

Statistical Analysis

We used the χ^2-tests to compare the two groups for categorical variables, Fisher's exact test for small data, and Mann-Whitney U test for continuous variables.

RESULTS

Eighty-four patients were enrolled in the trial. Forty (48%) had melioidosis. Twenty patients were assigned to each treatment group. The final analysis was done in 38 patients as two patients were excluded due to inadequate information.

Baseline Characteristics

Of a total of 38 patients with severe melioidosis, 19 received cefoperazone/sulbactam + co-trimoxazole and the other 19 ceftazidime + co-trimoxazole. The two treatment groups were well balanced with respect to demographic characteristics and underlying diseases (Table 1). The number of patients with disseminated septicemia was greater in the ceftazidime group than in the cefoperazone/sulbactam group (12 *vs* 7) but the difference was not statistically significant ($p > 0.05$) (Table 2). The distribution of sources of positive *B. pseudomallei* cultures and organ involvement is shown in Table 3. There were more cases

Table 1. Demographic data and underlying diseases of 38 cases of melioidosis.

	Treatment groups		Total
	Cefoperazone/Sulbactam n=19	Ceftazidime n=19	n=38
Sex Male :Female	16:3	12:7	28:10
Mean age (years) ± SD	47.9±12.5	52.1±10.9	50.2±11.8
Duration of symptoms			
< 2 weeks	7	7	14 (37%)
2-4 weeks	6	7	13 (34%)
> 4 weeks	6	5	11 (29%)
Underlying diseases	19	19	38 (100%)
Single	7	10	17 (45%)
Multiple	12	9	21 (55%)
Diabetes	11	1	22 (58%)
Renal insufficiency (Cr. > 2)	8	8	16 (42%)
Hematologic disease	5	3	8 (21%)
Previous melioidosis	2	5	7 (18%)

Table 2. Category of melioidosis.

	Treatment groups		Total
	Cefoperazone/Sulbactam n=19	Ceftazidime n=19	n=38
Disseminated septicemic form	7	12	19 (50%)
Non-disseminated septicemic form	7	4	11 (29%)
Severe localized form	5	3	8 (21%)

of positive pus cultures in the ceftazidime group ($p < 0.05$). However, clinical manifestations and laboratory findings on admission were similar in the two groups (Table 4).

Outcome

Three of the patients in the cefoperazone/sulbactam group died (16% mortality rate [95% confidence interval, 3.4% to 39.6%]) and 4 of the patients in the ceftazidime group died (21% mor-

Table 3. Source of positive culture and organ involvement of 38 cases of melioidosis.

	Treatment groups		Total	Exact
	Cefoperazone/Sulbactam n=19	Ceftazidime n=19	n=38	p-value
Source of positive culture				
Blood	13	14	27 (71%)	0.99
Sputum	6	6	12 (32%)	0.99
Urine	6	1	7 (18%)	0.09
Pus	6	13	19 (50%)	0.05
Others	0	3	3 (8%)	0.23
Organ involvement				
Single organ	10	7	17 (45%)	0.52
Multiple organs	8	12	20 (53%)	0.33
Lungs	11	9	20 (53%)	0.75
Musculoskeletal	4	10	14 (37%)	0.91
Spleen	5	6	11 (29%)	0.99
Skin & soft tissue	1	6	7 (29%)	0.09
Urinary tract	5	1	6 (16%)	0.18
Liver	2	1	3 (8%)	0.99

Table 4. Clinical and laboratory findings on admission.

	Treatment groups		Total
	Cefoperazone/Sulbactam n=19	Ceftazidime n=19	n=38
Clinical manifestation			
Fever (temperature >38°C	16	14	30 (79%)
Tachycardia (heart rate > 90/min)	15	15	30 (79%)
Dyspnea (respiratory rate > 20/min)	12	11	23 (61%)
Hypotension (systolic blood pressure < 90 mm Hg or > 40 mmHg reduction from baseline)	1	3	4 (10%)
Conscious change	4	5	9 (24%)
Presence of dissemination	7	9	16 (42%)
On respirator	4	2	6 (16%)
Laboratory findings			
Leukocytosis (wbc >10000/mm^3)	12	13	25 (66%)
Creatinine >2 mg/dl	12	9	21 (55%)
Prolonged prothrombine time	4	2	6 (16%)
Partial thromboplastin time	2	1	3 (8%)
SGOT[1] >40 U/L	13	16	29 (76%)
SGPT[2] >40 U/L	8	11	19 (50%)
Alkaline phosphatase >150 U/L	9	13	22 (58%)
Jaundice (total bilirubin >2 mg/dl)	7	8	15 (39%)

[1] SGOT (AST) = Serum aspartate aminotransferases
[2] SGPT (ALT) = Serum alanine aminotransferases

tality rate [95% confidence interval, 6.0% to 45.6%]). The difference between the two rates (p = 0.99) was therefore not significant enough to form a conclusion. The deaths in the cefoperazone/sulbactam group were caused by hospital-acquired *Klebsiella pneumoniae* septicemia (one case), severe sepsis with pneumothorax from melioidosis (one case), and severe melioidosis sepsis (one case). The deaths in the ceftazidime group were the result of severe melioidosis sepsis (three cases) and hospital-acquired *Klebsiella pneumoniae* and *Acinetobacter* species pneumonia (one case). Other clinical responses in terms of mean and median duration of defervescence, duration of parenteral treatment, and duration of admission were similar. There was no significant difference in bacterial clearance at 24 hours, 48 hours, and on day 6 (p = 0.99) (Table 5). Of the 11 patients in each group who had bacteremia, 8 (72%) had it cleared within 48 hours. One patient in the cefoperazone/sulbactam group had persistent bacteremia on the sixth day due to inadequate drainage of a shoulder joint.

Complications during treatment between the two treatment groups are shown in Table 6. There was less septic shock in the cefoperazone/sulbactam group (3 of 19 patients; 16%) than in the ceftazidime group (8 of 19 patients; 42%) although the difference was not statistically significant (p = 0.07). Septic shock in each group mostly developed in patients who had disseminated septicemia. Two cases (10%) in the cefoperazone/sulbactam group developed acute renal failure compared to 6 cases (31%) in the ceftazidime group (p = 0.23). Only three cases had coagulopathy during treatment - one in the cefoperazone/sulbactam group and the other two in the ceftazidime group.

Table 5. Clinical response and bacterial clearance.

	Treatment groups		p-value
	Cefoperazone/Sulbactam n=19	Ceftazidime n=19	
Mortality	3(16%)	4(21%)	0.99*
Mean duration of defervescence	8.21±7.69	10.0±9.94	0.84+
median (days)	7	8	
Mean duration of parenteral treatment	14.26±4.40	16.05±8.05	0.29+
median (days)	14	14	
Mean duration of admission	20.21±10.78	21.84±10.13	0.25+
median (days)	16	26	
Bacterial clearance in patients who had positive hemoculture			
	n=11	n=11	
in 24 hours	4	4	0.99*
in 48 hours	4	4	0.99*
in 6 days	2	3	0.99*
> 6 days	1	0	0.99*

* Fisher's Exact test
\+ Mann-Whitney U test

Table 6. Complications during treatment of melioidosis.

	Treatment group		p-value
	Cefoperazone/Sulbactam n=19	Ceftazidime n=19	
Septic shock	3(16%)	8(42%)	0.07
● disseminated	2/7	7/12	
● non-disseminted	1/7	1/4	
● severe localized	0/5	0/3	
Acute renal failure	2(10%)	6(31%)	0.23
Coagulpathy	1(5%)	2(10%)	0.99

Safety

One patient in the cefoperazone/sulbactam group developed autoimmune hemolytic anemia on the fifth day with positive direct Coomb's test. No blood transfusion was needed. The anemia resolved spontaneously after treatment was stopped.

DISCUSSIONS

This randomized, prospective study shows that low-dose parenteral cefoperazone/sulbactam + co-trimoxazole may be as effective as high-dose ceftazidime + co-trimoxazole in the treatment of severe melioidosis. The outcomes were similar in terms of mortality rate, bacterial clearance, mean and median duration of defervescence, and parenteral treatment. Patients treated with cefoperazone/sulbactam tended to suffer less septic shock than those treated with ceftazidime. These results, however, contradict the findings of an earlier study of ß-lactam + ß-lactamase inhibitor (amoxicillin/clavulanate) *vs* ceftazidime in the treatment of melioidosis[11]. In that study, there was no difference in the mortality rate between the two treatment groups but the clinical efficacy of amoxicillin/clavulanate in surviving patients was inferior. Patients who received amoxicillin/clavulanate had unsatisfactory responses, which required a change of antibiotic and a longer hospital stay. Furthermore, the dose of amoxicillin/clavulanate was very high - 160 mg/kg/day (1.2 g given every 4 hours). We believe that our better results can be attributed to the properties of both cefoperazone and sulbactam. Cefoperazone has its own activity on *B. pseudomallei* (unlike amoxicillin and ampicillin) and it has a long half-life, which means it can be administered every 8 to 12 hours. Sulbactam can inhibit ß-lactamase enzymes produced by *B. pseudomallei*[7].

The synergistic effect of combining cefoperazone and sulbactam was found in our *in vitro* study using E test (unpublished data). The MIC90 on 100 strains of *B. pseudomallei* dropped from 16 µg/ml when tested with cefoperazone alone to 3 µg/ml when tested with cefoperazone/sulbactam. It must be remembered, however, that this is the first clinical study of cefoperazone/sulbactam in the treatment of severe melioidosisis and is a preliminary one. A larger trial is needed to confirm these results. However, the results suggest that cefoperazone/sulbactam at a dose of 25 mg/kg/day of cefoperazone + co-trimoxazole is equally effective as ceftazidime for treating severe melioidosis.

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Cefoperazone/sulbactam ร่วมกับ co-trimoxazole เปรียบเทียบกับ Ceftazidime ร่วมกับ co-trimoxazole ในการรักษาโรคติดเชื้อ Melioidosis ที่รุนแรง

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ได้ทำการศึกษาแบบ prospective randomized double-blind controlled เปรียบเทียบ cefoperazone/sulbactam (cefoperazone 25 มก/กก/วัน ร่วมกับ co-trimoxazole (trimethoprim 8 มก/กก/วัน) กับ ceftazidime (100 มก/กก/วัน) ร่วมกับ co-trimoxazole (trimethoprim 8 มก/กก/วัน) ในการรักษาโรคติดเชื้อ melioidosis ที่รุนแรง การศึกษากระทำที่โรงพยาบาลศรีนครินทร์ มหาวิทยาลัยขอนแก่น ตั้งแต่เดือนกรกฎาคม พ.ศ. 2538 ถึงเดือนกันยายน พ.ศ. 2539 ในจำนวนผู้ป่วย 84 รายที่เข้าร่วมการศึกษา มี 40 ราย (ร้อยละ 48) ที่มีผลเพาะเชื้อขึ้น *Burkholderia pseudomallei* ซึ่งได้รับการสุ่มให้ได้รับยา 2 ชนิด และพบว่ามีผู้ป่วย 20 รายในแต่ละกลุ่ม ผู้ป่วย 2 รายไม่ได้นำมาวิเคราะห์ เพราะข้อมูลไม่ครบถ้วนซึ่งเป็นผู้ป่วย 1 รายในแต่ละกลุ่ม จากการศึกษาไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติในอัตราการตายของผู้ป่วยทั้ง 2 กลุ่ม คือร้อยละ 16 (3/19) ในกลุ่มที่ได้รับ cefoperazone/sulbactam และร้อยละ 21 (4/19) ในกลุ่มที่ได้รับ ceftazidime ($p > 0.05$) การตอบสนองโดยดูจากการขจัดเชื้อออกจากกระแสเลือดไม่แตกต่างกัน และไม่มีผลข้างเคียงรุนแรงในทั้ง 2 กลุ่ม ดังนั้น cefoperazone/sulbactam ร่วมกับ co-trimoxazole อาจใช้เป็นยาทดแทนในการรักษา melioidosis ที่รุนแรงได้ อย่างไรก็ตามควรมีการศึกษาที่ใหญ่กว่านี้เพื่อยืนยันผลการศึกษาครั้งนี้

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