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Multicenter Prospective Randomized Trial Comparing Ceftazidime plus Co-Trimoxazole with Chloramphenicol plus Doxycycline and Co-Trimoxazole for Treatment of Severe Melioidosis

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A prospective randomized trial was conducted at Srinagarind and Khon Kaen hospitals. Ceftazidime (100 mg/kg of body weight per day) and co-trimoxazole (trimethoprim, 8 mg/kg/day; sulfamethoxazole, 40 mg/kg/day) therapy was compared with conventional therapy (chloramphenicol, 100 mg/kg/day; doxycycline, 4 mg/kg/day; trimethoprim, 8 mg/kg/day; sulfamethoxazole, 40 mg/kg/day) in the treatment of 64 patients with bacteriologically confirmed cases of severe melioidosis who were admitted during September 1986 to January 1989. Of 61 evaluable patients (3 were excluded because of severe drug allergies), 42 were septicemic, and 31 of these patients had the most severe form, disseminated septicemic melioidosis. Their cumulative mortalities on day 7 were compared. There were significantly lower overall mortalities from melioidosis, septicemic melioidosis, and disseminated septicemic melioidosis in the group receiving the new treatment compared with those in the group receiving the conventional treatment (47 versus 18.5% [$P = 0.039$], 57.7 versus 25% [$P = 0.039$], and 82.3 versus 30.7% [$P = 0.006$], respectively); but the differences could have been influenced by the greater severity of illness, e.g., shock at initial presentation, in the patients who received the conventional treatment. Among patients with disseminated septicemia and initial shock, there was no significant difference in mortality between the regimens. Both regimens effectively eradicated bacteria from the circulation within 24 h (97 versus 96%, respectively). We recommend ceftazidime and co-trimoxazole as the drugs of choice for treatment of severe melioidosis, especially in those patients with disseminated septicemia.

Melioidosis, an infection caused by *Pseudomonas pseudomallei*, is highly endemic in southeastern Asia and northern Australia (3, 15, 18, 21, 24). Cases have been reported from at least 20 other countries, including North America, New Zealand, and West Africa (5, 8, 31). Thailand has by far the greatest number of cases, a high proportion of which are reported in the northeastern region, especially the provinces Khon Kaen and Ubon Ratchatani (23). It has been estimated that at least 1,000 cases of melioidosis have been diagnosed and treated in Khon Kaen since 1980 (30). Difficult diagnosis because of the protean clinical manifestation of the disease and a high mortality rate, despite conventional antimicrobial therapy, have been the major problems for physicians in endemic areas (18, 23). A new clinical classification of melioidosis has been developed (18, 23). It includes disseminated septicemic melioidosis, a rapidly fatal bacteremia with evidence of cutaneous or internal organ dissemination associated with 89% septic shock and 87% mortality; nondisseminated septicemic melioidosis, a fairly rapid progression of bacteremia with only single organ involvement associated with 5% septic shock and 17% mortality; localized melioidosis, a nonbacteremic slow progressive focal infection with 9% mortality; transient bacteremia; probable melioidosis; and subclinical melioidosis. Severe melioidosis would include disseminated septicemic, nondisseminated septicemic, and severe localized (a nonbacteremic focal infection with rapid progression and unstable vital signs) forms. Fatality generally occurs during the first 3 days of therapy. The currently recommended conventional antimicrobial agents (chloramphenicol, doxycycline, co-trimoxazole, kanamycin) are usually ineffective in patients with severe infections, and the mortality rate approaches 90%, despite therapy. These drugs are also associated with serious renal and hematological toxicities (18, 23). Ceftazidime has been recommended as the drug of choice for the treatment of melioidosis on the basis of its good in vitro activity against *P. pseudomallei* (2, 7) and previous successes with the drug in a few noncomparative therapeutic trials (23, 27). Our experience in an open multicenter trial also confirmed its efficacy and safety (20). Recently, ceftazidime and co-trimoxazole have been recommended for empiric use against septicemic melioidosis (26). We report here the results of a multicenter prospective randomized trial in which we compared a new regimen (ceftazidime and co-trimoxazole) with the conventional one (chloramphenicol, doxycycline, and co-trimoxazole) in the treatment of severe melioidosis. The therapeutic efficacies of the two regimens were compared by looking at the differences in the mortality rates within the first 7 days of therapy and the rates of bacterial clearance.

MATERIALS AND METHODS

The study was conducted at Srinagarind and Khon Kaen hospitals, Khon Kaen, Thailand, during September 1986 to January 1989. The patients enrolled in the study were aged 14 years or over and were clinically diagnosed with septicemia from a bacterial infection. They experienced moderate to severe clinical sepsis which was manifested by altered

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vital signs (pulse rate, >100/min; respiratory rate, >25/min; temperature, ≥38.5°C), impending shock (blood pressure, ≤90/60 mm Hg), respiratory failure, and evidence of dissemination of infection, e.g., blood-borne pneumonia, multiple cutaneous abscesses, or multiple abscesses in two or more internal organs. Patients were eligible for the study if they had two or more of these findings. They were excluded from the trial if they had an infection with an organism other than *P. pseudomallei* or an unrecognized organism, had been partially treated with antimicrobial agents which were active against *P. pseudomallei* (unless they had not responded unequivocally to the drugs), had a history of allergy to the study drugs or developed severe drug allergy during therapy, or there was in vitro resistance of the organisms causing their infection to ceftazidime or two of the drugs in the conventional regimen. Informed consent was obtained from either the patients or their guardians before the trial, and the human experimentation guidelines of the authors' institutions were followed in the conduct of the clinical research.

Study protocol. Upon entry into the study, the eligible patients received a thorough history and physical examination. Blood and urine samples were taken for laboratory tests, including complete blood count, urinalysis, blood sugar, blood urea nitrogen, creatinine, electrolytes, liver function tests, coagulogram, and *P. pseudomallei* indirect hemagglutination test (17). Attempts were made to find the source of infection. Cultures of blood, urine, or stool samples were prepared, and an abdominal ultrasound was performed if it was clinically indicated. Therapy was started as soon as the clinical specimens were taken. Patients were randomly assigned to receive either the new or the conventional regimen by use of a predetermined random number. The new regimen consisted of ceftazidime (100 mg/kg of body weight per day) given intravenously every 8 h, co-trimoxazole as trimethoprim (8 mg/kg/day), and sulfamethoxazole (40 mg/kg/day) given by intravenous drip every 8 h. The conventional regimen consisted of chloramphenicol (100 mg/kg/day) given intravenously every 6 h, doxycycline (4 mg/kg/day) given intravenously every 12 h, and co-trimoxazole as trimethoprim (8 mg/kg/day) and sulfamethoxazole (40 mg/kg/day) given by intravenous drip every 8 h. Parenteral therapy was given for at least 10 to 14 days and then was changed, if clinical improvement was achieved, to oral therapy with doxycycline and co-trimoxazole for both groups for at least 3 to 6 months. Most of the patients were nursed in an intensive care unit. Resuscitation of shock, acid-base imbalance, ventilatory support, surgical drainage of loculated pus, and other standard supportive therapy were performed during the study period. Close clinical evaluation was done by one of the investigators. A repeat single blood culture was done every 8 h on days 1, 2, 3, and 7. Those who were diagnosed as being infected with organisms other than *P. pseudomallei* were given the appropriate treatment. The endpoint of the trial was survival at 7 days and bacterial clearance on days 1, 3, and 7. Cumulative mortality and the rate of bacteremia up to day 7 for both regimens were analyzed statistically.

Bacteriology. Routine standard microbiological methods for culture of clinical specimens were used during the trial (13). In vitro antimicrobial susceptibility to the study drugs was determined by the modified Bauer-Kirby disk diffusion method (1, 14).

Statistical analysis. Study data were analyzed by the SPSS and Epistat programs by using the chi-square or Fisher exact tests for categorical variables and the unpaired Student *t* test for continuous variables. The level of significance was taken at $P \leq 0.05$. The Mantel-Haenzel chi-square test was used when adjustment was needed for confounding factors.

RESULTS

In order to show statistical significance for a 50% reduction or more of mortality in the group that received the new regimen, 20 cases of the most severe form of melioidosis (disseminated septicemia) in each group were required. The study was stopped after 28 months. One hundred thirty-six patients entered the trial; 64 of these patients were confirmed by bacteriological methods to be suffering from severe melioidosis. The other 72 patients were excluded with the following final diagnoses: nonclassified infections, 25 patients; bacterial infections, 23 patients (*Klebsiella* spp., 10 patients; *Escherichia coli*, 6 patients; *Staphylococcus aureus*, 3 patients; *Enterobacter* spp., 2 patients; *Salmonella* group B, 1 patient; pneumococcus, 1 patient); tuberculosis, 5 patients; leptospirosis, 3 patients; probable melioidosis, 2 patients; carcinomatosis, 5 patients; other noninfections, 9 patients. Three of 64 patients were subsequently excluded from the trial because of severe drug allergies during the trials (two patients who received the conventional regimen [one patient with severe hemolysis in glucose-6-phosphate dehydrogenase deficiency [G6PD], 1 patient with aplastic anemia caused by chloramphenicol]; 1 patient who received the new regimen [severe hemolysis in G6PD]). Of the 61 evaluable patients, 34 received the conventional regimen and 27 received the new regimen. Their demographic and baseline clinical and laboratory data were not different except for the rate of shock, the rate of respiratory failure, and creatinine and albumin levels; but they were not statistically significant (*P* values, 0.16 to 0.32) (Table 1).

Overall mortality in patients with severe melioidosis. Of the 61 patients suffering from severe melioidosis, 16 of 34 who received the conventional regimen and 5 of 27 who received the new regimen died within the first 7 days of treatment (47.0 versus 18.5%, respectively; $P = 0.039$) (Table 2).

Mortality in patients with severe melioidosis by their clinical classification. Of the 61 evaluable cases, 42 had positive blood cultures (septicemia) and were classified as suffering from disseminated septicemic (30 patients) or nondisseminated septicemic melioidosis (12 patients). The other 19 patients who were blood culture negative but clinically septicemic were classified as having localized melioidosis. Each group experienced initial shock (70, 16.6, and 42%, respectively), and the mortality rates were 60, 8, and 10%, respectively. Among the septicemic patients, 15 of 26 who received the conventional regimen and 4 of 16 who received the new regimen died ($P = 0.039$) (Table 2). Since the groups of patients with melioidosis were heterogeneous with regard to their prognoses, the most severe form, disseminated septicemic melioidosis, which causes the highest mortality, was our main concern. For the 30 patients with disseminated septicemic melioidosis, baseline demographic, clinical, and laboratory data were evenly distributed in all items except initial shock (15 of 17 patients in the group that received the conventional regimen versus 6 of 13 patients in the group that received the new regimen [$P = 0.012$]). Mortality rates were 14 of 17 in those who received the conventional regimen and 4 of 13 in those who received the new regimen (82.35 versus 30.76%, respectively, $P = 0.006$). Eighty-six percent of the overall mortality (18 of 21 patients) was contributed by this group, and so the cumulative survival curves of the two treatment groups of patients with disseminated septicemic melioidosis were plotted (Fig. 1). From

TABLE 1. Clinical features of the 61 patients with severe melioidosis

Characteristic[a]	Drug therapy[b]	
	Conventional regimen (n = 34)	New regimen (n = 27)
Age (yr)	45.6 ± 11.8	44.0 ± 12.4
Sex (no. M/no. F)[c]	21/13	18/9
Duration of illness		
Acute onset (≤7 days)	9	12
Subacute to chronic (>7 days)	24	13
Underlying diseases	28	23
Diabetes mellitus	19	16
Chronic renal failure	8	7
Clinical classification		
Disseminated septicemia	17	13
Nondisseminated septicemia	9	3
Localized	8	11
Multiorgan involvement	10	11
Initial shock	20	11
Respiratory failure	18	10
Laboratory		
Hematocrit (%)	32.2 ± 6.9	29.2 ± 8.4
Leukocytes (per mm^3)	11,694 ± 6,464	10,963 ± 5,429
Blood urea nitrogen (mg%)	50.2 ± 41.7	48.0 ± 39.9
Creatinine (mg%)	4.1 ± 4.4	2.9 ± 3.3
Albumin (g%)	2.9 ± 1.5	3.5 ± 2.5
Serum glutamic oxalacetic transaminase (sigma unit)	75.2 ± 71.3	70.5 ± 70.3
Serum glutamic pyruvic transaminase (sigma unit)	32.3 ± 18.4	30.2 ± 22.6
Alkaline phosphatase (sigma unit)	6.3 ± 4.8	4.7 ± 3.3

[a] None of the parameters was statistically different ($P > 0.05$).
[b] Conventional regimen, chloramphenicol, doxycycline, and co-trimoxazole; new regimen, ceftazidime and co-trimoxazole.
[c] M, male; F, female.

days 0 to 1, 5 of 17 patients in the conventional regimen group and 3 of 13 patients in the new regimen group died (P = 0.517); from days 2 to 7, 9 of 12 patients in the conventional regimen group and 1 of 10 patients in the new regimen group died (P = 0.003). Considering only patients with initial shock in the group with disseminated septicemic melioidosis, 13 of 15 patients who received the conventional regimen and 4 of 6 patients who received the new regimen died (86.6 versus 66.6%, respectively; P = 0.54). Covariate adjustment for initial shock by the Mantel-Haenzel chi-square test did not show a significant difference in mortality (P = 0.22) between the two regimens. Only one patient with disseminated septicemia developed late shock on day 3 of new regimen. He survived without a change of therapy. There were no mortality differences with other groups of melioidosis (Table 2).

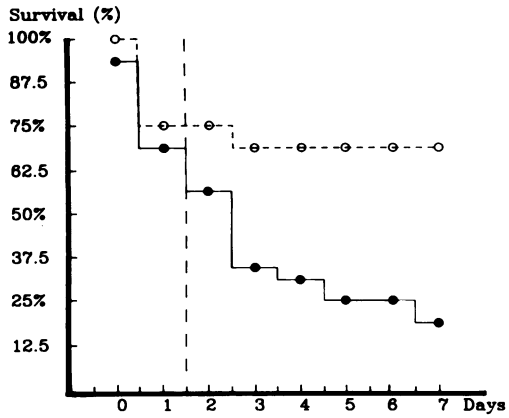

FIG. 1. Cumulative survival curves for patients with disseminated septicemic melioidosis after entry into the study. ○, ceftazidime and co-trimoxazole (n = 13); ●, conventional regimen (n = 17).

Complications caused by therapy. Two patients who received the conventional regimen and suffered from reversible hematological complications survived from disseminated septicemic shock and severe localized infection when therapies were changed to the new regimen on days 3 and 6, respectively. The other patient who had been on the new regimen developed severe hemolysis, which improved after co-trimoxazole was discontinued on day 3. The patient survived a severe localized infection after ceftazidime therapy. In addition to the three aforementioned cases that were excluded because of severe drug allergies, patients tolerated the new regimen very well. The nausea and vomiting in a few patients who received the conventional regimen were due to doxycycline.

Bacterial clearance. Bacterial clearance was achieved within 24 h for 33 of 34 isolates in patients in the conventional regimen group and 26 of 27 isolates in patients in the new regimen group. One isolate in a patient on the conventional regimen and another isolate in a patient on the new regimen were eradicated within 72 and 48 h, respectively.

Bacterial resistance. Eight clinical isolates were resistant to study drugs, two of which were multiply resistant strains (one was resistant to chloramphenicol and co-trimoxazole; one was resistant to chloramphenicol and kanamycin). They were resistant to ceftazidime (one isolate), and co-trimoxazole (four isolates), and chloramphenicol (four isolates). Patients with chloramphenicol- and co-trimoxazole-resistant strains received the new regimen, while the patient with a ceftazidime-resistant strain received the conventional regimen. Acquired resistance to the study drugs was not detected during the trial period.

Subsequent treatment and relapse. There were no deaths from infection after day 7. All of the patients from both groups who survived after day 7 were treated with oral doxycycline and/or co-trimoxazole for at least 3 to 6 months. There were no relapses during the 9 to 22 months of follow-up.

DISCUSSION

Melioidosis has become one of the most important public health problems in Thailand. Although there has been an increase in the bacteriological confirmation of diagnosis and early treatment of the disease, with the use of current

TABLE 2. Overall result of treatment of 61 patients with severe melioidosis with either the conventional or the new regimen

Regimen	No. of patients who died/total no. of patients (%) with the following:					
	Septicemia[a]	Disseminated septicemia	Nondisseminated septicemia	Severe localized	Localized	Total
Conventional	15/26 (57.6)	14/17 (82.3)	1/9	1/5	0/3	16/34 (47.0)
New	4/16 (25.0)	4/13 (30.6)	0/3	1/9	0/2	5/27 (18.5)
P	0.039[b]	0.006[b]	0.75	0.60	0.99	0.039[b]

[a] Total of disseminated and nondisseminated septicemia.
[b] Statistically significant ($P \leq 0.05$).

conventional antimicrobial therapy, mortality from severe melioidosis is still very high (6, 18, 23). Several limitations of such therapy, e.g., the bacteriostatic properties, in vitro antagonism and indifference of drug combinations, and potential serious toxicity, have been well documented (13, 23). Among the newly developed antimicrobial agents, piperacillin, imipenem, and ceftazidime have the lowest MICs for 90% of strains tested (0.5 to 2 μg/ml) (7, 19, 23, 29). Since our experience in treating moderate to severe cases of melioidosis with ceftazidime as a part of an open multicenter trial was excellent in terms of safety, clinical efficacy, and bacteriological response (20, 28), ceftazidime was chosen for use in our clinical trial. In addition to being an extracellular infection similar to that caused by other pseudomonads, melioidosis is also known to be an intracellular infection (11, 12, 16, 22). Since β-lactam antibiotics cannot, in general, penetrate well into cells (25), co-trimoxazole, the drug proven to be efficacious against certain intracellular pathogens (25) and melioidosis (18), was combined with other agents for use in a new regimen. At the time of this study, there were no reports which showed antagonism between ceftazidime and co-trimoxazole. In vitro antagonism between ceftazidime and sulfamethoxazole or trimethoprim but not co-trimoxazole has been demonstrated (10). A more recent study showed that there is no antagonism between ceftazidime and co-trimoxazole (4).

Our study confirmed the fact that severe melioidosis with clinical septicemia can be classified as various groups of diseases with different morbidities and mortalities. Ceftazidime and co-trimoxazole significantly reduced the overall mortality from severe melioidosis by 60.7% when it was compared with the conventional regimen ($P = 0.039$). Since the two groups were well matched in terms of clinical and laboratory parameters, it was concluded that the therapeutic efficacy of the new regimen is due to its better antimicrobial activity. When the clinical classification was taken into consideration, ceftazidime and co-trimoxazole significantly reduced the mortality from septicemic melioidosis by 56.6% ($P = 0.039$) when they were compared with conventional regimen. This therapeutic effect occurred only in patients with the most severe form of the disease (disseminated septicemic melioidosis) (62.2% reduction; $P = 0.006$). As shown in Fig. 1, the patients who received the new regimen had significantly lower mortalities than those who received the conventional regimen after 1 day (24 to 48 h) of therapy ($P = 0.003$). Indifferent mortalities during the first 24 to 48 h probably represented those who died before the onset of the therapeutic effects of the antimicrobial agents. Although it has not yet reached statistical significance, the new regimen showed a lower mortality among patients with disseminated septicemia with initial shock (23% reduction; $P = 0.54$). Even though almost all bacterial isolates were eradicated within the first 24 h by both regimens, half of the fatalities occurred after this, possibly suggesting that the cause of death in patients with severe melioidosis is not directly or solely related to the organisms in the circulation. A primary ceftazidime-resistant strain was isolated from a patient who had disseminated septicemia with initial shock and who died 48 h after receiving the conventional regimen.

Results of this study indicate that ceftazidime and co-trimoxazole are more efficacious than the conventional regimen in treating severe melioidosis, especially in patients who present with disseminated septicemic melioidosis. We suggest that the role of the conventional regimen should be limited to use against the mild to moderately severe forms of the disease.

White et al. (32) have recently advocated the use of ceftazidime as a monotherapy for severe melioidosis. Certain advantages of the ceftazidime–co-trimoxazole combination over ceftazidime monotherapy included a more rapid bacterial eradication rate (100% eradication versus 20% noneradication within 48 h [32]) and a lower relapse rate over the period of follow-up. Lately, while there has been no acquired ceftazidime-resistant *P. pseudomallei* in our hospitals, Dance et al. (9) have experienced more of this problem in their institution during the past few years, after their original clinical trial.

Antimicrobial resistance has been a serious problem in Thailand. Combining ceftazidime with co-trimoxazole and emphasizing the clinical conditions in which the new regimen is truly indicated might help to eliminate this problem.

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