รายงานวิจัยฉบับสมบูรณ์

โครงการ “การศึกษาเปรียบเทียบประสิทธิภาพของยา cefotaxime, doxycycline และ penicillin G ในการรักษาผู้ป่วยสงสัยโรคเลปโตสไปโรซิสที่มีอาการรุนแรง”

โดย รองศาสตราจารย์แพทย์หญิงยุพิน ศุพุทธมงคล และคณะ

วันที่ 12 ธันวาคม 2546

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สำนักงานกองทุนสนับสนุนการวิจัย

(ความเห็นในรายงานนี้เป็นของผู้วิจัย ผู้ให้ทุนไม่จำเป็นต้องเห็นด้วยเสมอไป)

An Open Randomized Controlled Trial of Penicillin, Doxycycline, and Cefotaxime in Patients With Severe Leptospirosis

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Keywords: Leptospirosis, penicillin, doxycycline, cefotaxime

Short title: Antimicrobial therapies in leptospirosis

Footnote: This study was funded by Thailand Research fund, The Ministry of Public Health Thailand, and the Wellcome Trust of Great Britain. Parenteral doxycycline used in this study were donated from Charles Knirsch (Pfizer Pharmaceutical, NY). Wirongrong Chierakul and N J. White are supported by the Wellcome Trust of Great Britain.

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ABSTRACT

An open label randomized comparison of parenteral doxycycline, cefotaxime, and penicillin G in suspected severe leptospirosis was conducted in 540 patients admitted to four hospitals in North Eastern Thailand. Of these 252 (47%) had serological or culture confirmed leptospirosis. Overall mortality was 4.8%. There were no significant different between the antibiotics in mortality, defervescence or time to resolve laboratory overall, or in the subgroup of patients with confirmed leptospirosis. Rickettsial infection was diagnosed in 132 patients, and in these patients doxycycline was superior to penicillin. Doxycycline or cefotaxime are satisfactory alternatives to penicillin for treatment of severe leptospirosis.

INTRODUCTION

Leptospirosis is an acute febrile illness caused by infection with pathogenic spirochetes of the genus *Leptospira*. It is a zoonosis of worldwide distribution [1]. Leptospirosis is considered to be an emerging infectious disease in many countries including Thailand [2-4]. Before 1996, less than 200 cases were diagnosed annually in this country. Since then there has been a marked rise in the annual number of reported cases between 2,000- 13,000 cases and 200- 500 deaths each year [4]. The epidemic has affected the North and North East of the country [5]. Clinical manifestations of leptospirosis are non-specific, varying from subclinical infection, a self-limited anicteric febrile illness with or without meningitis, to a severe and potentially lethal multisystem illness with jaundice, renal failure, and pulmonary hemorrhage in many fatal known as Weil's syndrome. The mortality associated with severe leptospirosis may be as high as 15% [1]. The manifestations of severe leptospirosis initially are similar to other community-acquired septicemia or severe manifestations of other common tropical infections including scrub typhus and malaria. The lack of reliable laboratory diagnosis has been an important problem.

There is scanty information on the treatment options for severe leptospirosis [6]. Penicillin G sodium is the generally recommended treatment of severe leptospirosis at any stage of the disease. But penicillin G has a narrow antimicrobial spectrum, it is not active against many of the important bacterial pathogens causing systemic illness in northeastern Thailand. Cefotaxime, a broad-spectrum third generation cephalosporin, is widely available highly active against leptospires in vitro and in an animal studies. The MIC_{50} against several serovars of leptospires varied between 0.05-0.1 microgram/ml [7]. Doxycycline is also active against leptospires, has been used for the prophylaxis and treatment of mild leptospirosis [8, 9]. Doxycycline is also active against scrub typhus, an important cause of fever in rural areas of Asia. Both cefotaxime and doxycycline are well-tolerated and

potentially alternative treatments for severe leptospirosis. We report here results of a multi-center open randomized control study to compare the efficacy and tolerability of cefotaxime, parenteral doxycycline to penicillin G sodium in the treatment of suspected leptospirosis.

PATIENTS AND METHODS

Study site and patients This study was conducted between July 2001- December 2002 at four hospitals in northeastern Thailand; Udornthani Hospital, Udornthani Province; Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima Province, Loei Hospital, Loei Province and Ban Mai Chaiyapod Hospital, Bureerum Province. Inclusion criteria were

(1) clinically suspected leptospirosis (acute fever, conjunctival suffusion, headache, muscle tenderness, jaundice);

(2) no primary focus of infection such as pneumonia, urinary tract infection.

The following patients were excluded from the study; children less than 15 years old, pregnant or lactating women, diabetic patients, known to have allergy to any of the study medications and definite history of treatment active against leptospirosis for more than 48 hours. This study protocol was approved by the Ethics Review Subcommittee of the Ministry of Public Health, Thailand. Informed consent was obtained from all patients or their guardians before entered the study.

Randomization and Study protocol: After enrollment patients were randomly allocated to receive one of the study drugs. Each study hospital had an independent random allocation number set, which was enclosed in a sealed opaque envelope. The penicillin G group (group P) received 1.5 million unit of intravenous penicillin G sodium (Government Pharmaceutical Organization, Thailand) every 6 hours. The cefotaxime group (group C) received 1 g of cefotaxime (Siam Pharmaceuticals, Thailand) every 6 hours. The doxycycline group (group D) received 200 mg of doxycycline (Pfizer Pharmaceutical, NY) infusion in 30 minutes, followed by 100 mg infusion every 12 hours. Gentamicin combination was also

administered in patients in group P and group D for whom septicemia due to gram-negative pathogens could not be initially excluded. Gentamicin therapy was discontinued as soon as blood cultures were negative. Parenteral treatment was continued until the patient was well enough to switch to oral therapy. They were then switched to either oral amoxicillin 2 g per day (group P and group C) or oral doxycycline 200 mg per day (group D). The total duration of treatment was 7 days. Other aspects of fluid balance management and patient care were similar in the three treatment groups.

Detailed history, physical examinations and laboratory investigations were recorded into the same standard form. Baseline investigations included a full blood cell and platelet count, two blood cultures (5-ml of blood in 50 ml of brain-heart infusion medium for routine aerobic bacteria and 5- ml of blood in sterile heparinized bottle for leptospires culture), plasma glucose, electrolytes, serum urea, creatinine, liver function tests, a urine analysis and chest radiography. The 5-ml heparinized blood was stored at room temperature, and then 100, and 500 µl was used for leptospires culture in EMJH medium. At least two sera, on admission and at 2- 4 weeks out-patient follow-up visit were taken and stored at -20^0C until serology was performed at the Faculty of Medicine Siriraj Hospital, Mahidol University and the National Institute of Health, Ministry of Public Health Thailand. All sera were tested for the serological diagnosis of leptospirosis, scrub typhus, murine typhus and dengue infection as described previously [1, 10-12].

These hospitals lie outside the malaria endemic area, but malaria was excluded if there was a history of recent travel. The isolation of leptospires from blood or a fourfold or greater rise in the agglutinin antibody titer (using microagglutination test, MAT) or in the specific IgG and IgM antibody titers (using the indirect immunofluorescent antibody test, IFAT) to at least 1: 200, or a single titer or stable antibody titer of 1: 400 or more was considered a definite serological diagnosis of leptospirosis. Criteria for the diagnosis of

rickettsial infections (scrub typhus, murine typhus, and spotted fever groups) were either at least fourfold rise in specific anti-rickettsial IgG or IgM (using IFAT) titer between paired serum samples to a titer of at least 1:200, or a single titer or stable IFA titer of 1: 400 or greater. Dengue infection was diagnosed by the specific IgM and IgG enzyme linked immunosorbent assay (ELISA) as described previously.

Patients with confirmed leptospirosis were classified prospectively into mild and severe leptospirosis. Severe disease was defined by at least one organ system dysfunction manifest by hypotension (systolic blood pressure of < 90 mmHg or a sustained decrease in systolic BP $\geq$ 40 mmHg); hepatic dysfunction (a rise in total bilirubin to ≥50 μmol/L (normal range 5.1- 17 μmol/L), or aminotransferase levels either aspartate (AST) or alanine (ALT) to ≥120 U/L (normal range 0- 40 U/L), or alkaline phosphatase to ≥ 350 U/L (normal range 39- 117 U/L), oliguria (urine output < 0.5 ml/kg/hr for at least one hour), or azotemia (serum creatinine of ≥ 266 μmol/L); decrease mental activity; requirement for mechanical ventilation, or hemorrhagic complications such as hemoptysis, or gastrointestinal bleeding).

Statistical analysis: The incidence of leptospirosis was 30-40% among patients with acute febrile illness whom leptospirosis was suspected. The mean (SD) duration of defervescence was 4.7 (4.2) days in a previous study [13]. Thus total of 160 patients in each group was required to detect a 40% reduction in fever clearance from 5 to 3 days in the penicillin group compared to either the doxycycline or cefotaxime treatments with 95% confidence and 90% power. Descriptive statistics used to summarize the demographic and baseline data in each study group. Differences between groups were analyzed by the chi-square test for categorized variables and the Kruskal- Wallis H test for continuous variables. Outcomes were compared between each treatment group and multivariate analysis was used to compare the efficacy of the three antibiotic treatments.

The efficacy of the three study drugs was analyzed both on the overall treatment groups (i.e. on an intention to treat basis of including all randomized patients and grouping them according to randomization groups) as well as in two subgroup analyses on patients who had serologically confirmed leptospirosis, and those with rickettsial infections with or without leptospirosis co-infection. For all analyses for fever clearance, patients who died within the first 48 hours of admission were excluded. The duration of fever was measured from the time of the first dose of antimicrobial therapy to the last recording of a temperature of > 37.5^0C. The fever resolution in each treatment group was compared by Kaplan- Meier plot and log-rank tests. The duration for which serum creatinine levels were raised was taken as time from day of admission to the study until the last recorded abnormal serum creatinine level (> 133 μmol/l). The duration for which serum total bilirubin and/ or aminotransferase levels/ and or alkaline phosphatase levels were raised was taken as time from day of admission to the study until the last recorded abnormal level.

RESULTS

Overall 540 patients entered the study. The male: female ratio was 6:1. The median (range) age of the patients was 36 (13- 92) years. The median duration of fever was 3 (range 1- 14) days before admission into the hospital. The demographic data, duration of illness, severity of illness characterized by number of vital organ dysfunctions, and distributions of the final diagnosis between the three study groups were similar (data not shown here). The diagnosis of leptospirosis was confirmed in 252 patients (46.7%). Leptospires were isolated from blood cultures obtained on admission from 41 (16.3%) patients (17 in group P, 13 in group D, and 11 in group C respectively). The proportion of patient with coincident rickettsioses, mainly scrub typhus, was similar in the three study groups. Two patients had both leptospirosis and bacteremia from Gram-negative bacilli (one patient had both leptospiremia and *Salmonella* Group D bacteremia, and another patient had 4-fold rising of

agglutinin antibody to *Leptospira interrogans* serovars grippotyphosa to a titer of 1: 400 and *Klebsiella pneumoniae* bacteremia).

There were 26 (4.8%) deaths in this study (9 patients in group P, 7 patients in group C, and 10 patients in group D). There was no difference between the treatment groups (P=0.82). The diagnoses of these fatal cases were leptospirosis in 7, septicemia due to other bacteria (or other bacterial infection with secondary sepsis) in 5, scrub typhus, leptospirosis and scrub typhus co-infection in one each. A definite diagnosis was not obtained in 12 patients who died. Twenty patients were excluded from the subsequent efficacy analysis; 11 patients who died within 48 hours after admission (5 patients in group P, 3 patients in group D and group C respectively), 6 patients due to inappropriate randomization (2 patients in group P, 2 patients in group D, and 2 patients in group C respectively), and 1 patient in group D and 1 patient in group C because they were referred to other hospitals before the final outcomes were known. The demographic data and baseline information, and distribution of their diagnoses compared between the three study groups are shown in table 1 and the laboratory investigations are shown in table 2.

Outcomes of treatment

a) All randomized patients

Overall outcomes of treatment (mortality and clinical treatment failure, duration of fever, and duration of organ dysfunction after treatment) were similar in the three treatment groups. The mortality was 2.3%, 2.4%, and 3.9% in group P, group D, and group C respectively (P=0.62). There were 10 patients with community- acquired bacteremia from other bacteremia (*E. coli* in 2 patients, *K. pneumoniae* in 2 patients, *Salmonella* Group D in 2 patients, *B. pseudomallei* in 2 patients, and *Streptococcal spp*. in 2 patients) entered into the study. Four of them died (2 patients with *E. coli* bacteremia, 1 patient from *K. pneumoniae* bacteremia, and 1 patient from *B. pseudomallei* bacteremia). The mean

(95%CI) duration of fever clearance after treatment was 72 [64-80] hours in group P, 72 [64-80] hours in group D, and 60 (50-70) hours in group C, respectively; P= 0.25). A Kaplan-Meier plot comparing the duration of fever clearance between the three treatment groups is shown in figure1.

In the penicillin treated group, additional antimicrobial therapy was given to 26 patients; 3 patients with leptospirosis for the treatment of hospital acquired infection, and 23 patients with an inadequate clinical response after at least 48 hours of penicillin treatment (4 patients with leptospirosis, 12 patients with rickettsioses or rickettsioses and leptospirosis co-infection, 6 patients with other diagnoses, and 1 patient with leptospirosis and *K. pneumoniae* bacteremia).

In the doxycycline treated group, additional antimicrobial therapy was given to 17 patients (in 2 patients with leptospirosis and in 2 patients with rickettsioses for the treatment of hospital acquired infection, and in 13 patients because of an inadequate clinical response after at least 48 hours of doxycycline treatment (4 patients with leptospirosis, 3 patients with rickettsioses or rickettsioses and leptospirosis co-infection, 5 patients with other diagnoses, and 1 patient with leptospirosis and *Salmonella* Group D bacteremia).

In the cefotaxime treated group, additional antimicrobial therapy were given to15 patients; 1 patient with leptospirosis for the treatment of hospital acquired infection, and 14 patients due to inadequate clinical response after at least 48 hours of cefotaxime treatment (4 patients with leptospirosis, in 4 patients with rickettsioses, and in 6 patients with other diagnoses).

Complications after in treatment developed in 75 patients; 31 (18%) in group P, in 24 (14.4%) patients in group D, and 20 (11%) group C respectively (P=0.18). Of these 25% developed dysfunction in two or more vital organ systems. Major complications were respiratory failure including pulmonary hemorrhage in 41 patients, hypotension or acute

myocarditis in 18 patients, hepatic dysfunction in 9 patients, multiorgan failure developed in 5 patients, and renal dysfunction in 3 patients.

b) Patients with confirmed leptospirosis

There were 241 patients with confirmed leptospirosis included in this analysis (76 patients in group P, 78 patients in group D, and 87 patients in group C, respectively). Demographic data were similar in the three treatment groups. The male to female ratio was 7:1. The median duration of fever before admission was 3 days (range 1- 14 days). Overall 75% of these patients presented with early onset i.e. duration of fever less than 5 days prior to admission (77.6% in group P, 76.9% in group D, and 71.3% in group C respectively, P=0.58). However there was no statistical significant difference in the duration of fever clearance after treatment between the early and late onset groups (P=0.58).

Most patients (202 patients, 83.8%) in this study had evidence of at least one vital organ dysfunction, and 57 (23.7%) patients developed multi-organ dysfunction before admission (table 3). The mean (95%CI) duration of fever after treatment was associated significantly with the extent of organ dysfunction on admission; 46 (36-95) hours in patients without any organ dysfunction, 64(55-72) hours in patients with one vital organ system dysfunction, 82 (67-97) hours in patients with 2 vital organ systems' dysfunction, and 71 (54- 88) hours in patients with multiorgan dysfunction (P =0.03).

Only five patients died (2 patients in group P, and 3 patients in group D). Three cases died from multi-organ failure and 2 patients died from pulmonary complications. The mean duration (95%CI) of fever after each treatment was 72 (95% CI 65- 79) hours in group P, 72 (50- 94) hours in group D, 60 (49- 72 hours in group C, P= 0.59). The Kaplan- Meier plot comparing the fever clearance of the three treatment groups is shown in figure 2. There was also no statistical difference in the duration of renal and/ or hepatic dysfunction in these patients treated with either penicillin G, or doxycycline, or cefotaxime.

Multivariate analysis was used to predict duration of fever after treatment, adjusted for onset (early or late), severity of leptospirosis on admission (number of vital organ system dysfunction), and antimicrobial treatment. Patients with two or multiorgan dysfunction on admission was significantly associated with longer duration of fever after treatment when compared to the other two groups (P=0.01). Antimicrobial therapy (P= 0.81) and onset of disease (P=0.71) were not associated with duration of fever after treatment in this model.

c) Patients with rickettsioses

There were 132 patients with rickettsioses with or with out leptospirosis infection entered into this study (42 in group P, 44 patients in group D, and 46 patients in group C respectively). The proportion of leptospirosis and rickettsial infection co-infection (45.2% in group P, 39.1% in group D, and 34.1% in group C respectively), scrub typhus (19% in group P, 32.6% in group D, and 38.6% in group C respectively), murine typhus (14,3% in group P, 8.7% in group D, and 6.8% in group C respectively) and spotted fever group (21.4% in group P, 19.6% in group D, and 20.5% in group C respectively) were similar in the three study drug groups (P= 0.56).

In this subgroup analysis, penicillin was significantly less effective than doxycycline and cefotaxime for the treatment of patients with rickettsioses. The treatment failure rates were 30.9%, 4.3%, 11.4% in group P, group D, and group C respectively (P =0.002). Overall only 1 patient who was randomized to penicillin G treatment died. He had leptospirosis and scrub typhus co-infection with hepatic and renal dysfunction on admission. He died 10 days after treatment and the most likely cause of death was intracerebral hemorrhage.

In the penicillin treated group, 13 patients were switched to other antimicrobial therapy, mainly doxycycline or chloramphenicol because of the clinical treatment failure (one of whom died). In the doxycycline treated group, only 2 patients were switched to

other antimicrobial treatments; adequate clinical response in 1 patient, and the development of adverse event (rash) in another patient. In the cefotaxime treated group, 5 patients were switched to other antimicrobial treatments because of an inadequate clinical response.

DISCUSSION

There has been an epidemic of leptospirosis in Thailand since 1996. The clinical investigators in this study were all very familiar with leptospirosis, which become a major cause of rainy season admission to hospital in the endemic areas of North and North East Thailand. However this study clearly demonstrates the difficulty in making a correct clinical diagnosis of this infection even for experienced clinicians. Approximately half of the patients with clinically suspected leptospirosis had laboratory confirmation for their diagnosis. Co-infection of leptospirosis and rickettsioses was also confirmed to be common in rural Thailand. This is not surprising as wet rice paddies provide a suitable habitat for these organisms and their hosts. Two documented cases of leptospirosis and other bacteremia were found in this study. A definite diagnosis could not be obtained in about 20% of the patients in this study despite extensive laboratory investigations.

The laboratory diagnosis of leptospirosis is still problematic. False negative antibody test, using any genus specific test currently available, is well recognized. Most patients in this study came to the hospital at the early stage of leptospirosis because they were all aware of the epidemic of leptospirosis in the region, increasing the opportunity for antimicrobial treatment to prevent progression to fatal disease [14, 15]. In very few places are diagnostic test results available on the day of admission to hospital. Limitations in both the clinical and laboratory diagnosis of leptospirosis in patients admitted with potentially life threatening infection prompted us to conduct this study to evaluate empirical antimicrobial therapies in patients with suspected leptospirosis. The results of this study showed that doxycycline and cefotaxime were as effective as penicillin G for the treatment of

leptospirosis. The mortality, duration of fever, and progression of vital organ dysfunction were similar in the three study groups, both in suspected and confirmed leptospirosis. The three treatments were equally well tolerated. The stage of illness (early or late presentation) was not associated with duration of fever in this study, whereas the severity of disease was. The results suggested that antimicrobial treatment was also beneficial in late stage leptospirosis because clinical responses such as the duration of fever and organ dysfunctions after treatment were similar to those came in at the early stage.

Empirical treatment with doxycycline instead of penicillin G had the additional benefit of efficacy in patients with rickettsioses whom initially diagnosed as suspected leptospirosis. Interestingly cefotaxime appeared to be better than penicillin in this group, although given the lack of activity against these intracellular bacteria, this may have been a chance finding.

Although the overall mortality was low in this study, the mortality in 10 patients with suspected leptospirosis that was diagnosed subsequently as community- acquired bacteremia was 40%. Two of these patients were randomized to penicillin and doxycycline. In the cefotaxime treated group, there were also 4 patients with community-acquired bacteremia initially diagnosed as suspected leptospirosis, two of them died despite (*K. pneumoniae* bacteremia, and *B. pseudomallei* in 1 each) cefotaxime treatment.

Penicillin G remains an effective treatment of leptospirosis. The mean duration of fever after penicillin treatment was similar to that in a recent report from Thailand [16]. However its use, as an initial empiric treatment in patients with suspected leptospirosis, might not be appropriate where a definite diagnosis cannot be made rapidly. In this circumstance, especially in patients whom the serological diagnosis for leptospirosis was negative on admission, antimicrobial therapy with either doxycycline or cefotaxime or the two antibiotics combined would be preferable. More clinical studies to evaluate for simple

clinical and laboratory parameters to differentiate rickettsial infections from leptospirosis are needed urgently.

ACKNOWLEDGEMENT

We are very grateful to Professor Ralph Corey for his help, Prof Didier Raoult for providing all antigens of spotted fever group rickettsioses used in this study. The authors thank Professor Amorn Leelarasamee, Head of the Department of Medicine; Professor Somwang Danchaivijitr, Head of the Division of Infectious Diseases and Tropical Medicine, Mahidol University, Faculty of Medicine Siriraj Hospital; Directors of Udornthani Hospital, Udornthani Province; Maharaj Nakhon Ratchasima Hospital, Nakhon Ratchasima Province, Loei Hospital, Loei Province and Ban Mai Chaiyapod Hospital, Bureerum Province for their permission to conduct this study; doctors, nurses, and medical technologists of these four hospitals for their cooperation and help during the study period. Ms. Saowaluk Silpasakorn for conducting of all indirect immunofluorescent tests for leptospirosis, and rickettsial infection. Mrs. Watcharee Ong and Ms. Duangdao Waywa for data entry and check.

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Table1. Demographic data, clinical presentations and final diagnosis compared between the three study groups.

	Group P (n= 172)	Group D (n= 167)	Group C (n= 181)	P-value
Male/female	154/18	144/23	151/30	0.25
Median age in year (range)	36 (13-92)	35 (15-75)	37 (15-71)	0.80
Median days of illness (range)	3 (1-11)	3 (1-15)	4 (1-15)	0.07
Previous antimicrobial therapy (%)	65(37.8)	69 (41.3)	72 (39.8)	0.80
Clinical syndrome on admission (%)				0.64
- Acute febrile illness	40 (23.3)	42 (25.1)	44 (24.3)	
- One organ dysfunction	46 (26.7)	58 (34.7)	60 (33.1)	
- Two organ dysfunction	49 (28.5)	38 (22.7)	46 (25.4)	
- Multi-organ dysfunction	37(21.5)	29(17.4)	31 (17.1)	
Bleeding complications				
- Yes (%)	28 (16.3)	19 (13.8)	17 (9.4)	0.21
Final diagnosis (%)				0.55
- Leptospirosis	76 (44.2)	78 (46.7)	87 (48.1)	
- Rickettsioses	23 (13.4)	28 (16.8)	29 (16.0)	
- Leptospirosis+ rickettsioses	19 (11.0)	18 (10.8)	15 (8.3)	
- Leptospirosis+ other bacteremia	1 (0.6)	1 (0.6)	-	
- Other diagnosis				
- Other bacterial Infection	4 (2.3	8 (4.8)	9 (5.0)	
- Viral infection	10 (6.4)	3 (1.8)	5 (2.8)	
- Unknown	42(23.3)	34(19.5)	37(19.9)	

Table 2.Laboratory investigations on admission compared between the three study groups.

Median (range)	Group P	Group D	Group C	P-value
WBC > 12,000/cu.mm., %	32.3	36.9	36.6	0.62
Thrombocytopenia*, %	34.6	34.6	39.9	0.52
Serum creatinine, µmol/L	133 (62-1,197)	115 (62-1,153)	133 (44-1,117)	0.08
Total bilirubin, µmol/L	22.1 (1.7-890.8)	20.4 (1.7-744.6)	23.8 (3.4- 642.6)	0.49
AST, U/L	60 (13-568)	59 (10-5865)	48 (13-627)	0.37
ALT, U/L	44 (3-2,750)	43 (2-4,695)	41 (6-478)	0.25
Alkaline phosphatase, U/L	122 (21-1,156)	126(20-965)	136(20-1,082)	0.98

* platelet count <100,000/cu.mm.

Table 3. Demographic data, clinical presentations of patients with laboratory confirmed leptospirosis compared between the three study groups.

	Group P (n= 76)	Group D (n= 78)	Group C (n= 87)	P-value
Male/female	66/10	71/7	73/14	0.39
Median age in year (range)	35 (13-70)	33 (15-61)	35 (16-70)	0.67
Median days of illness (range)	3 (1-11)	3 (1-10)	3 (1-14)	0.34
Previous antimicrobial therapy (%)	29 (38.2)	28 (35.9)	31 (35.6)	0.94
Clinical syndrome (%)				0.16
- Acute febrile illness	10 (13.2)	17 (21.8)	12 (13.8)	
- One organ dysfunction	18 (23.7)	29 (37.2)	33 (37.9)	
- Two organ dysfunction	26 (34.2)	16 (20.5	23 (26.4)	
- Multi-organ dysfunction	22 (28.9)	16 (20.5)	19 (21.8)	
Laboratory investigations				
- WBC > 12,000/cu.mm., n (%)	23 (31.5)	30(39)	31 (36.9)	0.62
- Thrombocytopenia, n (%)	29 (42)	27 (37.5)	38 (47.5)	0.46
Median (range) of				
- serum creatinine, µmol/L	142(71-1,197)	124 (71-763)	142 (44-1,020)	0.16
- Total bilirubin, µmol/L	28.9(1.7- 589.9)	22.1 (3.4- 550.8)	23.8 (3.4-642.6)	0.23
- AST, U/L	68 (13-327)	53 (10-519)	47 (17-627)	0.10
- ALT, U/L	42 (4-152)	44 (6-567)	42 (6-478)	0.54
- Alkaline phosphatase, U/L	123 (21-593)	106 (27- 793)	139 (36-630)	0.54

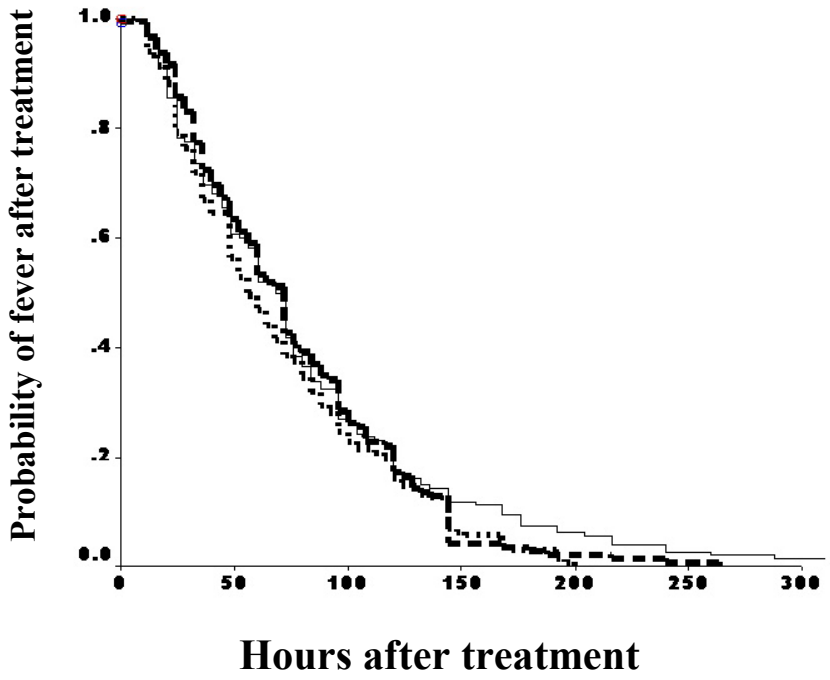

Figure 1. Kaplan- Meier plot of the duration of fever after treatment among all randomized patients compared between the three treatment groups (— group P, - - - group D, and ⋯ group C respectively).

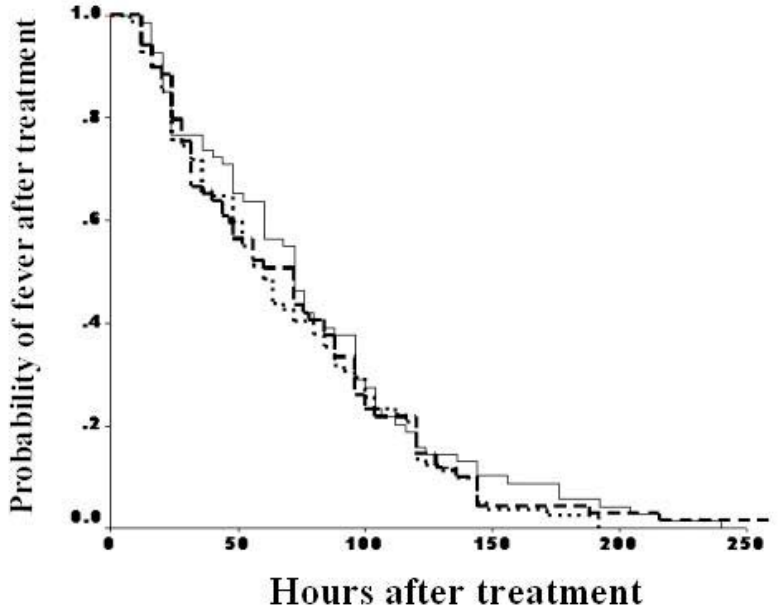

Figure 2. Kaplan- Meier plot of the duration of fever after treatment in patients with leptospirosis compared between the three treatment groups (—group P, −−group D, and ⋯ group C respectively).

รหัสโครงการ : RDG3/13/2544

ชื่อโครงการ : การศึกษาเปรียบเทียบประสิทธิภาพของยา cefotaxime, doxycycline และ penicillin G ในการรักษาผู้ป่วยสงสัยโรคเลปโตสไปโรซีสที่มีอาการรุนแรง

ชื่อผู้วิจัยหลัก : ยุพิน ศุพุทธมงคล [1], กรรณิการ์ นิวัตยะกุล [2], ชวนพิศ สุทธินนท์ [3], กิตติ โล่สุวรรณรักษ์ [4], รุ่งเรือง ลิ้มไพบูลย์ [5], วิรงรองค์ เจียรกุล [6], วรรณพร วุฒิเอกอนันต์ [6], สุรภี เทียนกริม [1], มงคล เจนจิตติกุล [7], นิโคลัส เจ ไวท์ [6]

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ระยะเวลาโครงการ : สิงหาคม 2544 – สิงหาคม 2546

บทคัดย่อ : การศึกษาทางคลินิกเพื่อเปรียบเทียบประสิทธิผลและความปลอดภัยของการรักษาผู้ป่วยที่มีภาวะไข้เฉียบพลันและสงสัยโรคเลปโตสไปโรสีสที่มีอาการรุนแรงด้วย
ยาด็อกซี่ซัยคลิน และยาเส็พโฟแท็กซีม กับยาเพ็นนิซิลิน ที่โรงพยาบาลศูนย์อุดรธานี จังหวัดอุดรธานี โรงพยาบาลมหาราชนครราชสีมา จังหวัดนครราชสีมา โรงพยาบาลเลย จังหวัดเลย และโรงบ้านใหม่ไชยพจน์ จังหวัดบุรีรัมย์ ระหว่างเดือนกรกฎาคม พ.ศ. 2544 ถึงเดือนธันวาคม พ.ศ. 2545 มีผู้ป่วยในโครงการทั้งสิ้น 540 รายและเสียชีวิต 26 ราย (ร้อยละ 4.8) ในจำนวนนี้เป็นผู้ป่วยโรคเลปโตสไปโรสีสจำนวน 252 ราย ผลการรักษาด้วยยาทั้ง 3 ชนิด (อัตราตาย ระยะเวลาที่หายไข้หรือระยะเวลาที่การทำงานของตับหรือไต กลับเป็นปรกติหลังการรักษา) ไม่แตกต่างกันทั้งในกลุ่มผู้ป่วยทั้งหมดและผู้ป่วยที่เป็นโรคเลปโตสไปโรสีสเท่านั้น อย่างไรก็ตามพบว่า ยาด็อกซี่ซัยคลินให้ผลการรักษาดีกว่ายาเพ็นนิซิลินในผู้ป่วยที่เป็นโรคสครับทัยฟัสที่ได้รับการวินิจฉัยทางคลินิกเมื่อแรกรับไว้ในโรงพยาบาลว่าเป็นโรคเลปโตสไปโรซีส โดยสรุปการศึกษาครั้งนี้พบว่า ยาด็อกซี่ซัยคลิน และยาเส็พโฟแท็กซีม เป็นยาที่สามารถเลือกใช้ในการรักษาผู้ป่วยโรคเลปโตสไปโรสีสแทนยาเพ็นนิซิลินได้อย่างมีประสิทธิภาพ

คำหลัก : เลปโตสไปโรสิส, เพ็นนิซิลิน, ด๊อกซี่ซัยคลิน, เส็ฟโฟแท็กซิม

Project Code : RDG3/13/2544

Project Title : A Comparative Study of the Efficacy of Cefotaxime and Doxycycline and Penicillin in the Treatment of Severe Leptospirosis.

Investigators : Yupin Suputtamongkol [1], Kanigar Niwatayakul [2], Chuanpit Suttinont [3], Kitti Losuwanaluk[4], Roongroeng Limpaiboon [5], Wirongrong Chierakul [6], Vanaporn Wuthiekanun [6], Surapee Triengrim[1], Mongkol Chenchittikul[7], Nicholas J White [6, 8]

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Project Duration : August 2544 – August 2546

Abstract : An open label randomized comparison of parenteral doxycycline, cefotaxime, and penicillin G in suspected severe leptospirosis was conducted in 540 patients admitted to four hospitals in North Eastern Thailand. Of these 252 (47%) had serological or culture confirmed leptospirosis. Overall mortality was 4.8%. There were no significant different between the antibiotics in mortality, defervescence or time to resolve laboratory overall, or in the subgroup of patients with confirmed leptospirosis. Rickettsial infection was diagnosed in 132 patients, and in these patients doxycycline was superior to penicillin. Doxycycline or cefotaxime are satisfactory alternatives to penicillin for treatment of severe leptospirosis.

Keywords : Leptospirosis, penicillin, doxycycline, cefotaxime