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MAINTENANCE THERAPY OF MELIOIDOSIS WITH CIPROFLOXACIN PLUS AZITHROMYCIN COMPARED WITH COTRIMOXAZOLE PLUS DOXYCYCLINE

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Abstract. This is a report of a randomized, open, labeled study of the maintenance treatment of melioidosis using a combination of ciprofloxacin and azithromycin (Regimen A) for 12 weeks versus a combination of cotrimoxazole and doxycycline (Regimen B) for 20 weeks. The study was conducted at two tertiary-care hospitals in northeast Thailand. A total 65 patients were enrolled, 36 and 29, respectively, between August 1997 and July 1998. Subjects were randomly allocated to each arm of the trial, resulting in 32 treated under Regimen A and 33 in B. The main outcome was a culture-proven relapse in melioidosis. There were more relapses under Regimen A at 22% (7 of 32) than in Regimen B, 3% (1 of 33). The 19% difference in the rates was significant (95% confidence interval [CI]: 3% to 34%; exact *P*-value = 0.027). Based on our data, a combination of cotrimoxazole and doxycycline treatment for 20 weeks should be given further consideration as the maintenance therapy of choice for melioidosis.

INTRODUCTION

Melioidosis is an infectious disease caused by the gram-negative bacterium, *Burkholderia pseudomallei* (formerly *Pseudomonas pseudomallei*). Clinical manifestations of melioidosis are protean, ranging from localized infection to overwhelming septicemia. The treatment of melioidosis is problematic, not only in the acute phase when mortality is high, but also in the maintenance phase when long-duration antibiotic therapy is required to prevent a relapse. The rate of relapse during maintenance treatment of melioidosis is 23% even with combinations of cotrimoxazole, doxycycline, and chloramphenicol,[1] or high doses of amoxycillin and clavulanate given for 8 weeks.[2] Maintenance therapy with ciprofloxacin or ofloxacin has failure rates of 29%,[3] and doxycycline alone has a relapse rate of 26%.[4] The reasons for the high relapse rate are the ability of the organism to survive within phagocytic cells,[5] the production of glycocalyx, and the formation of microcolonies in infected tissues.[6]

An *in vitro* study showed that the biofilm of a normally ceftazidime- and cotrimoxazole-susceptible strain of *B. pseudomallei* is highly resistant to ceftazidime and cotrimoxazole.[7] Vorachit and others[8] found that *in vitro* the combination of ciprofloxacin and azithromycin had a cidal effect against *B. pseudomallei.* Yasuda and others[9] reported a synergistic effect both *in vitro* and *in vivo* of quinolone and macrolide in the elimination of the biofilm produced by *Pseudomonas aeruginosa.* Theoretically, the combination of ciprofloxacin and azithromycin should be an effective treatment of melioidosis since ciprofloxacin has a bactericidal and lasting post-antibiotic effect,[10] and both have good penetration into phagocytic cells[11,12] which might eliminate or inhibit the production of glycocalyx. In Thailand, a three-drug regimen, the combination of cotrimoxazole plus doxycycline, without chloramphenicol during the first month of treatment, is the commonly used alternative to the conventional four-drug regimen. The reason is the concern for potential bone marrow suppression by chloramphenicol. A prospective study of this three-drug versus the conventional four-drug regimen for the maintenance therapy of melioidosis is underway. The present study was a prospective, open, randomized trial comparing oral ciprofloxacin with azithromycin and oral cotrimoxazole with doxycycline as a maintenance treatment for melioidosis.

MATERIALS AND METHODS

The study was conducted in tertiary care hospitals in northeast Thailand: Sapprasitthiprasong Hospital in Ubon Ratchatani province, and Srinagarind Hospital in Khon Kaen province. Enrollment of the patients was done between August 1997 and July 1998. The final analysis was carried out in March, 1999.

Patient selection and treatment. Patients were 14 years of age or older with culture-proven melioidosis. Informed consent was obtained from all patients or their guardians before they were entered into the study which was approved by the Ethical Review Board of Khon Kaen University. Patients with a history of allergic reactions to any of the experimental drugs, pregnant or lactating women, and those unable to return for follow-up were excluded.

After enrollment, patients were randomly allocated to treatment Regimen A or B. Regimen A consisted of ciprofloxacin (Ciprobay®: Bayer at 20 mg/kg/d, usual dose 500 mg twice daily) and azithromycin (Zithromax®: Pfizer 500 mg daily) for 12 weeks. Regimen B consisted of cotrimoxazole (10 mg trimethoprim + 50 mg sulfamethoxazole kg/d, usual dose 2 single tablets twice daily) and doxycycline (Vibramycine®: Pfizer at 4 mg/kg/d, usual dose l00 mg twice daily) for 20 weeks.

Follow-up and outcome. Patients were asked to attend follow-up every 4 to 6 weeks during treatment and thereafter every 4 to 8 weeks. At every visit, symptoms of the disease or side effects of treatment were recorded and a physical examination, a complete blood count, a renal function test, and a liver function test were performed. Patients were asked to bring back any remaining medication to check for compliance. Further investigations were carried out if the test results were abnormal or as otherwise clinically indicated. The primary outcome measure—a microbiological failure—was the number of culture-proven relapses during or after

TABLE 1
Baseline clinical data

	Oral treatment	
	Regimen A*	Regimen B†
No. of patients (N = 65)	32	33
Males : females	20:12	21:12
Mean age (SD) yr	51 (12)	49 (13)
Melioidiosis category		
Disseminated septicemia melioidosis§	14	10
Non-disseminated septicemia melioidosis¶	3	1
Multifocal localized melioidosis#	5	4
Localized melioidosis	10	18
Blood culture positive	17	11
Underlying disease		
None	3	7
Diabetes mellitus	22	21
Renal failure	7	5
Renal stone	5	2
Other	7	6
Median duration of initial parenteral treatment (d)‡	14 (1–32)	15 (1–45)
Ceftazidime given for initial treatment	24 (75%)	20 (61%)
Median duration of oral treatment (d)‡	82 (16–174)	137 (32–163)
No. who completed treatment (%)	26 (81%)	26 (79%)
Median duration of follow-up (d)‡	220 (40–501)	277 (55–533)

* Ciprofloxacin plus azithromycin
† Cotrimoxazole plus doxycycline
§ Blood culture positive with disseminated infection
¶ Blood culture positive with one focus of infection or none
# Multifocal infection without positive blood culture
‡ Range in parenthesis
d = days

therapy. The secondary outcome measure—a clinical failure—was the number of persistent infections observed clinically without culture-proven evidence. Overall treatment failure was defined as either clinical or microbiological failure.

Statistical analysis. All analyses were performed on an *intention-to-treat* basis. These included data for all subjects who met the eligibility criteria, were enrolled in the study, and received at least one dose of test medication. Means, standard deviations, minima, maxima, and medians were presented for the continuous data. Proportions were provided for the categorical data. The magnitude of the treatment effect was estimated using the difference between two proportions and its 95% confidence intervals. The Mantel-Haenszel χ^2 test was used because the study had two sites. The Fisher exact test was used because of the small sample size. A multiple logistic regression was used to test the effect of blood culture results, disseminated disease, and hospital site, and the likelihood ratio (LR) test was used to assess the probability of those variables.

RESULTS

Baseline characteristics. Thirty-six (55%) melioidosis-proven cases were enrolled from Sapprasitthiprasong Hospital and 29 (45%) from Srinagarind Hospital. Of the total, 32 were treated with Regimen A and 33 with Regimen B. The baseline demographic data, clinical category, number of patients with a positive blood culture, underlying diseases, initial parenteral treatment (type of antibiotic and duration), number of patients who completed the oral treatment, and duration of follow-up were similar for both groups (Table 1). The incidence of underlying diseases such as diabetes mellitus, renal failure, and renal stones was also similar in both groups. Most patients received ceftazidime as the initial parenteral treatment (75% in Regimen A versus 61% in Regimen B). The median duration of 82 days (range 16 to 174 days) for the oral treatment in Regimen A was shorter than the 137 days (range 32 to 163 days) for Regimen B, according to the study protocol. Most (81%) of cases treated with Regimen A and 79% treated with Regimen B completed the treatment. The median duration for follow-up was 220 days (range 40 to 501 days) in Regimen A compared with 277 days (range 55 to 533 days) in Regimen B.

Outcome. The outcome of treatment is summarized in Table 2. Eight patients had microbiological failure: 22% (7 cases) in Regimen A and 3% (1 case) in Regimen B. The 19% difference in the failure rate was significant (95% CI: 3% to 34%, exact $P = 0.027$). The one patient in Regimen B who suffered a relapse had a persistent positive culture during oral treatment.

Among the seven relapsed cases in Regimen A, three occurred during treatment (one was fatal) and the other four relapsed after completing their treatment. Two of them underwent an extended course of treatment (17 and 20 weeks).

Two patients in each regimen had clinical failure. Both cases in Regimen A completed 12 weeks of treatment but the splenic abscesses did not resolve. In Regimen B, one patient developed a pleural effusion with a negative culture during treatment, and the other developed small abscesses in the liver and spleen even after completing 20 weeks of treatment (a culture was not obtained). Overall we experienced treatment failure in nine cases (28%) in Regimen A and three (9%) in Regimen B. The 19% difference being significant (95% CI: 1% to 37%, exact $P = 0.048$).

Mortality. Two patients in each of the regimens died during the study. One patient from Regimen A died from a

TABLE 2
Outcome of melioidosis maintenance therapy study (N = 65)

Outcome	Regimen A* n = 32	Regimen B† n = 33	Difference	95% Confidence interval	*P*-value
Microbiological failure	7 (22%)	1 (3%)	19%	3.4%–34.3%	0.027
Treatment failure	9 (28%)	3 (9%)	19%	0.6%–37.4%	0.048

* Ciprofloxacin plus azithromycin
† Cotrimoxazole plus doxycycline

relapse of melioidosis whereas the other died from a squamous cell carcinoma after completing treatment for melioidosis. In Regimen B, one patient died from lung cancer during treatment and the other from *Eschericia coli* septicemia after completing treatment.

Adverse drug reactions. There were similar adverse drug reactions in the two treatment groups. Three and four patients in Regimens A and B, respectively, developed rash with pruritus. The symptoms were severe enough to discontinue or change treatment. One of four patients in Regimen B who developed a rash also had a history of doxycycline photosensitivity. The other patient from Regimen B reported mild abdominal discomfort, but no change in dosage was required.

DISCUSSION

Conventional maintenance therapy with the combination of cotrimoxazole, doxycycline, and chloramphenicol given for 20 weeks significantly decreases the relapse rate of melioidosis to 4%.[13] However, compliance with the long course of antimicrobial treatment is poor, and only 56% of patients complete the 20-week treatment.[13] Although oral fluoroquinolones and newer macrolides have intermediate and low activity against *B. pseudomallei,* they have excellent intracellular penetration.[11,12] *Burkholderia pseudomallei* is known to survive inside phagocytic cells,[5] to produce glycocalyx and to form microcolonies in infected tissue.[6] An *in vitro* study showed that the combination of ciprofloxacin and azithromycin (Regimen A) had a cidal effect against *B. pseudomallei*.[8] In an animal model, quinolone and macrolide had a synergistic effect in the elimination of the biofilm produced by *P. aeruginosa.* Therefore, a combination of ciprofloxacin and azithromycin with a shorter course was evaluated in this open but randomized and otherwise controlled study.

We found that treatment with a combination of ciprofloxacin and azithromycin (Regimen A) led to a higher rate of microbiological-proven relapses (22% versus 3%, $P = 0.027$) and had a higher total treatment-failure rate (28% versus 9%, $P = 0.048$) than cotrimoxazole plus doxycycline (Regimen B). This difference was also demonstrated in the survival analysis ($P = 0.052$, data not shown).

The difference in the outcomes of the regimens cannot be explained by differences in compliance since 82% and 79% of the patients in Regimens A and B, respectively, completed their therapy. An extension of treatment with ciprofloxacin and azithromycin would not be likely to decrease the relapse rate, because two out of four cases relapsed, even when treatment continued for 17 and 20 weeks.

The effect of blood culture and disseminated disease on the effect of drug on relapse was assessed using a logistic regression, and neither variable was statistically significant. So the magnitude of the treatment remained unchanged. Taking into account the effect of blood culture, the magnitude of effect based on the odds ratio (OR_{DRUG}) changed from 8.96 to 9.27, and the likelihood ratio (LR) test *P*-value was 0.444. For the effect of disseminated disease, the OR_{DRUG} changed from 8.96 to 9.27 and the LR test also was not significant ($P = 0.750$). The combined effects were also not significant ($P = 0.576$). The effect of hospital site was minimal (OR_{DRUG} changed from 8.96 to 9.24, LR test P-value = 0.576). Therefore, we need not adjust for these effects.

In our study, the combination of ciprofloxacin and azithromycin had a similar response rate as that reported for a previous study of fluoroquinolones alone (ciprofloxacin or ofloxacin) in the maintenance treatment of melioidosis,[3] with an overall failure rate of 27% versus 29%, respectively. Our study also shows the low relapse rate (3%) of the three-drug regimen as compared to that of the conventional four-drug regimen which was 4%.[13]

The ineffectiveness of azithromycin added to the regimen at a later stage of infection (i.e., the maintenance-treatment phase) may be because it is too late to prevent the formation of glycocalyx. During the early course of melioidosis, organisms disseminate and form small abscesses throughout the internal organs. They might already have formed microcolonies and produced glycocalyx. Whether or not initiating azithromycin treatment during the acute treatment would prevent glycocalyx formation and decrease the relapse rate needs further investigation.

In conclusion, the results of our study show that in the maintenance therapy of melioidosis, the combination of cotrimoxazole and doxycycline given for 20 weeks should be given consideration as the treatment of choice. Ciprofloxacin given with azithromycin is not recommended because it produced no detectable results.

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