Scrub Typhus: Single Oral Dose Doxycycline Therapy in Mild to Moderately Severe Cases

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Abstract

A single oral dose of 200 mg of doxycycline was shown to be effective in the treatment of patients with scrub typhus. Sixty patients fulfilled our inclusion criteria for diagnosis of scrub typhus; forty-two were treated with single oral dose of 200 mg of doxycycline. Thirty-seven of these patients recovered completely within 72 hours of treatment giving the response rate of 88.1%. There were no documented cases of relapses within the one-month period after treatment.

INTRODUCTION

Scrub typhus is an infectious disease caused by *Rickettsia tsutsugamushi*. This disease is prevalent in Asia-Pacific region including Thailand where it occurs predominantly in North-eastern and Northern parts. Standard treatment for scrub typhus is the use of 500 mg of tetracycline or chloramphenicol six hourly for 5–7 days or until the patient is afebrile for at least 24 hours. Sheehy et al, in 1973, found that tetracycline eliminated symptoms and signs of scrub typhus more rapidly than chloramphenicol and relapse was uncommon unless treatment was started too early. In the treatment of louse-borne typhus, Krause et al in 1975 used a single dose of 100 to 200 mg of doxycycline, a long-acting derivative of oxytetracycline, and found that it was as effective as a 10 day-course of tetracycline or chloramphenicol. Doxycycline then was used in the treatment and prophylaxis of scrub typhus. At first, doxycycline was administered intravenously in the treatment of scrub typhus. This parenteral form is not available in most parts of Thailand, therefore, therapeutic trial with oral form is more convenient. In this study, we report the efficacy of single oral dose doxycycline therapy for mild to moderately severe cases of scrub typhus admitted to Maharaj Nakorn Chiang Mai Hospital.
MATERIALS AND METHODS

Patients

Patients of at least 15 years of age admitted to the Department of Medicine, Maharaj Nakorn Chiang Mai Hospital, Thailand, between June 1988 and December 1988, with the diagnosis of scrub typhus, were included in the study.

The diagnostic criteria for scrub typhus included; (1) presence of fever and clinical features suggestive of scrub typhus such as headache, cough, conjunctival injection, lymphadenopathy, hepatomegaly; (2) presence of eschar; and (3) positive WeiI-Felix test; i.e., an OX-K titre of 1:320 or more, or a fourfold rising titre in the convalescent serum. Diagnosis of scrub typhus was made when the patient had criterion 1 plus at least one of criteria 2 and 3.

Patients with scrub typhus who tolerated oral administration were given 200 mg of doxycycline as a single oral therapy.

Patients were excluded for the following reasons; previous tetracycline or chloramphenicol therapy in the period of less than 2 weeks prior to the study; a history of allergy to tetracycline; severe manifestations including shock, meningitis, disseminated intravascular coagulation, myocarditis, respiratory failure, and adult respiratory distress syndrome; pregnancy; or if the patients had severe vomiting.

Laboratory methods

Hematology

Three occasions of thick film examination for malarial parasites were performed within 72 hours of admission. Complete blood counts were determined on the first and tenth days of admission.

Bacteriology

Blood and urine were taken for bacteriologic isolation in all patients and sputum in some patients with cough or dyspnea.

Biochemistry

Blood chemistry was determined for renal and liver functions in all patients and repeated periodically if any abnormality was detected.

Serology

Acute and convalescent serum samples were tested for rickettsial disease (WeiI-Felix test), typhoid fever (Widal test), and leptospirosis (macrohemagglutination test).

Clinical evaluation

Patients were observed for 14 days from the start of therapy and scheduled to return for observation approximately 1 month after treatment. Patients who could not stay in hospital for 2 weeks were allowed to be discharged when they were afebrile for at least 48 hours and scheduled to return on

the 14th and 30th days. Temperature recordings were made four hourly by the nursing staff, and the patients were visited once daily by a doctor in the study group.

End points of study were:
- improvement, i.e.
  - disappearance of all symptoms within 72 hours of therapy; and
  - defervescence within 72 hours of therapy
- failure, i.e.
  - no improvement of symptoms within 72 hours of therapy; or
  - persistent fever for more than 72 hours after treatment; or
  - clinical deterioration during observation

Any patient who failed to respond to doxycycline therapy was given 500 mg of chloramphenicol six hourly for 7 days.

RESULTS

Patient characteristics

A diagnosis of scrub typhus was made in 60 patients during the study period of 7 months. Thirty-six were male and 24 were female. Mean age of the patients was 34 years with a range of 15 to 74. Diagnostic criteria were fulfilled in all patients (Table 1).

Of the 41 patients (68.3%) who had positive WeiI-Felix test, 14 had eschars. All the patients who were negative for WeiI-Felix test (19 of 60, or 31.1%) had eschars.

Eighteen patients were excluded from the study; 9 cases because of severe manifestation; and 9 because of previous tetracycline or chloramphenicol therapy. Forty-two patients

Table 1 Criteria for diagnosis in 60 cases of scrub typhus

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Number of patients (%)</th>
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<tbody>
<tr>
<td>1 plus 2</td>
<td>33 (55)</td>
</tr>
<tr>
<td>1 plus 3</td>
<td>41 (68.3)</td>
</tr>
<tr>
<td>1 plus 2 plus 3</td>
<td>14 (23.3)</td>
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<tr>
<td>Total</td>
<td>60 (100)</td>
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Table 2 Response to single oral dose doxycycline therapy

<table>
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<tr>
<th>Disappearance of all Symptoms Number (%)</th>
<th>Defervescence Number (%)</th>
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<tr>
<td>Within 24 hours 32 (76.2)</td>
<td>22 (52.4)</td>
</tr>
<tr>
<td>Within 48 hours 37 (88.1)</td>
<td>31 (73.8)</td>
</tr>
<tr>
<td>Within 72 hours 41 (97.6)</td>
<td>37 (88.1)</td>
</tr>
<tr>
<td>Total 42 (100)</td>
<td>42 (100)</td>
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without any exclusion criterion were enrolled to the study.

Response to treatment

Of the 42 patients receiving single oral dose doxycycline therapy, response to treatment was demonstrated in Table 2.

Thirty-seven of 42 patients (88.1%) were without fever and any symptom within 72 hours of therapy. Five patients (11.9%) failed to respond to doxycycline therapy, four of these still had high grade fever and were given 500 mg of chloramphenicol six hourly for seven days, all of them recovered uneventfully. We decided to continue observing the other patient who was clinically stable despite low grade fever which subsided on the fifth day of treatment without any additional therapy.

Relapse

Only 20 of 38 cases (52.6%) who recovered with single oral dose doxycycline therapy returned for follow-up one month after treatment. No relapse was documented in any of these cases.

DISCUSSION

This study was among the first efficacy studies of doxycycline in the treatment of scrub typhus in Thailand. A single oral dose of 200 mg of doxycycline was shown to be effective. Eighty-eight percent of patients treated with this regimen improved within 72 hours of therapy. Although there was no control group treated with standard therapy for comparison in the study, one trial by Brown et al in Malaysia in 1978 concluded that the single oral dose of 200 mg of doxycycline was as effective as a seven-day course of tetracycline 500 mg six hourly.3 In addition, our study, as well as previous study by Brown et al,3 showed that relapses were uncommon following this regimen of therapy. Therefore, we suggest that, unless there is any contraindication, patient with scrub typhus, particularly in the absence of severe manifestations, should be treated with single oral dose of 200 mg of doxycycline. This therapeutic regimen is effective, inexpensive, and can be given on an outpatient basis. Furthermore, patient compliance for this regimen is better than the seven-day standard therapy.

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REFERENCES