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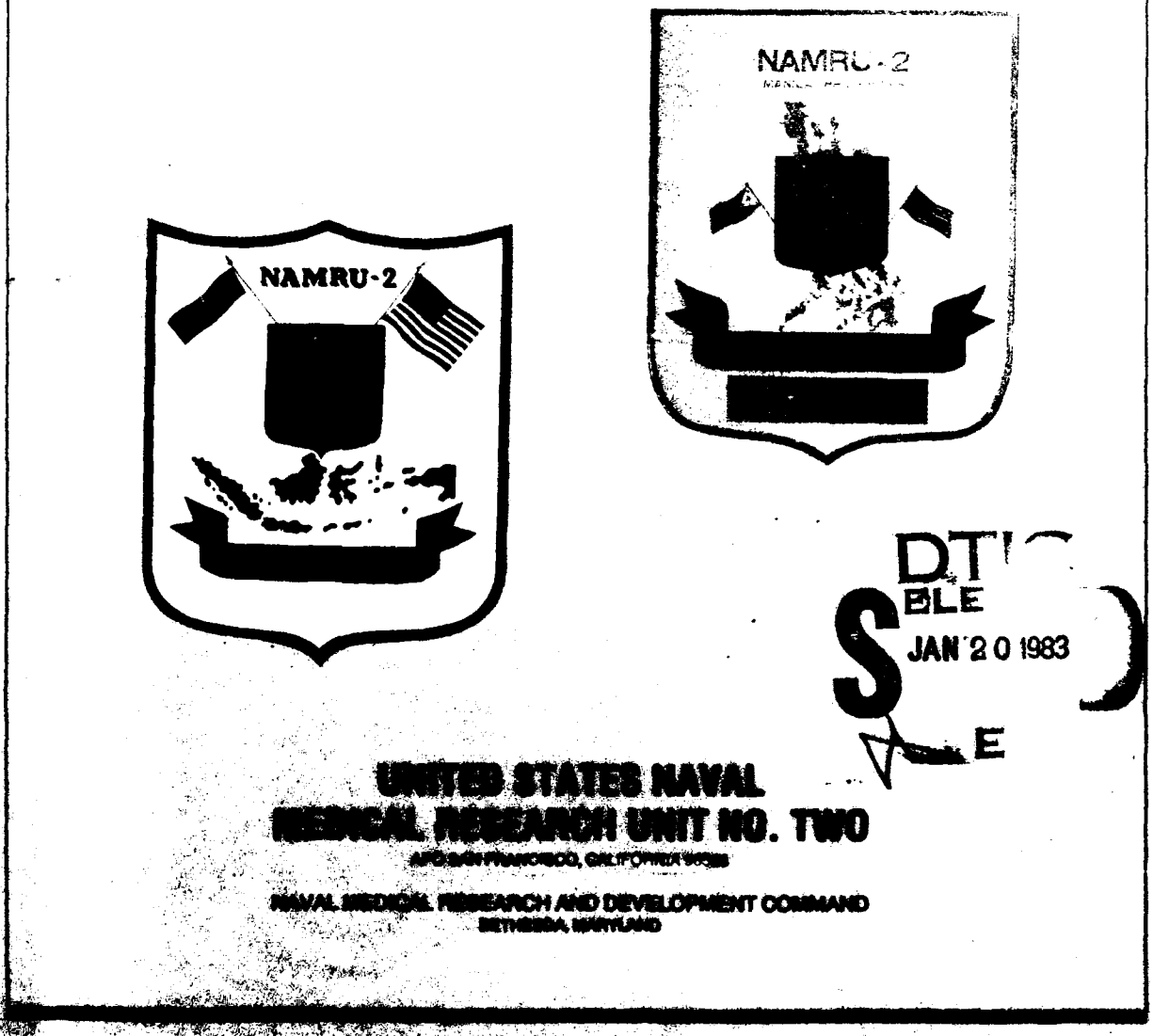

RISK OF RELAPSE ASSOCIATED WITH DOXYCYCLINE THERAPY FOR SCRUB TYPHUS[1]

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I. INTRODUCTION

Chloramphenicol (Chloromycetin) or oxytetracycline (Terramycin) are the drugs presently recommended for treatment of patients with scrub typhus (1). These antibiotics are usually given in 250 mg doses every 6 hrs for 5 to 7 days. Since both drugs are rickettsiostatic, relapses can occur following initial treatment unless follow-up antibiotics are administered (2-4).

Scrub typhus outbreaks have occurred in nonimmune military populations whose occupational exposures increased their risk of infection with Rickettsia tsutsugamushi (5,6). Under field conditions, simpler methods of treatment of shorter duration would provide great advantage to medical and paramedical personnel responsible for treatment.

Doxycycline (Vibramycin), a lipophylic congener of oxytetracycline, is rapidly and completely absorbed from the gut and maintains high levels in the blood for several days following administration (7). It is a candidate antibiotic for single dose therapy for scrub typhus. Single doses of doxycycline are effective in the treatment of epidemic louse-borne typhus (8) and are effective in the treatment of scrub typhus in rural populations of Malaysia (9). The present study compares the effectiveness of single and weekly-spaced doses of doxycycline with multiple doses of oxytetracycline in a double blind, randomized trial conducted in a population of scrub typhus patients who were exposed in the Pescadores Islands of Taiwan.

II. MATERIALS AND METHODS

The study population was comprised of 68 Chinese military personnel from Taiwan who were stationed in the Pescadores Islands in 1976, were admitted to the Penghu Naval Base Hospital with suspected scrub typhus and whose illnesses were confirmed by laboratory means. Subjects were all males, mostly young army recruits who had not previously been exposed to R. tsutsugamushi infections. The epidemiology of scrub typhus in the Pescadores Islands has been discussed elsewhere (10,11).

Patients were acutely ill when they were admitted to the hospital. Most were in early stages of their disease (mean days between onset and treatment was 5.4 days). Oral temperatures were 38C or greater in 66 of 68 patients, all had eschars and two-thirds had typical scrub typhus rashes. Patients were examined by a physician before treatment and then twice daily while they remained in the hospital for 3 weeks. The diagnosis

of scrub typhus was confirmed by recovering rickettsiae (12) from venous blood collected before antibiotic therapy was begun or by demonstrating a 4-fold increase in antibody from the acute to the convalescent phase of illness by the indirect immunofluorescence method of Bozeman and Elisberg (13) as modified by Bourgeois et al. (10).

Patients were randomly allocated to one of three treatment regimens as follows: doxycycline, 200 mg in a single dose on day 1 of treatment, followed by placebo (DXY I, 22 patients); doxycycline, 200 mg in a single dose on day 1, followed by placebo and a second 200 mg dose of doxycycline on day 7 (DXY II, 23 patients); oxytetracycline, 500 mg every 6 hrs for 7 days (OXY, 23 patients). Drug and placebo were manufactured in such a way and administered every 6 hrs for 7 days so that neither patient nor physician knew to which regimen a given patient was assigned. Randomization was forced in 3 groups and stratified by age to ensure that the groups were of a comparable age distribution.

Cure was defined as a prompt relief of symptoms and a return to normal health using trial treatment only; persons with recrudescent but self-limited fevers (1 or more measurements of 37.6 C on 2 or more consecutive days) were included in this group. Recurrence of fever and other symptoms severe enough to require treatment was classified as a relapse. Two patients vomited shortly after drug administration, had a continuation of symptoms and were considered primary treatment failures. Those patients who experienced relapses and who vomited their drug were retreated with oxytetracycline 500 mg given orally at 6-hr intervals for 7 days.

III. RESULTS

Table 1 shows the categories of patient response. Two persons who received doxycycline vomited their first drug dose. These patients were excluded from further analysis but were treated with oxytetracycline and promptly cured. All other patients initially responded to antibiotic therapy satisfactorily. Mean times from treatment to return to normal temperature were the same for each group. In general, signs and symptoms disappeared quickly. Most patients were up and about on the third day of study and could have returned to their units for convalescence on day 5-7 following treatment. There were no instances of pneumonitis, encephalitis, heart failure or bleeding. Symptoms persisted for about equal periods in the 3 treatment groups.

TABLE 1. Frequency of Response among Scrub Typhus Patients by Treatment Group

Treatment group	Primary treatment failure	Relapse	Initial Cure with recurrence of fever	Uncomplicated cure	Total
Doxycycline, single dose (200mg)	0	2 (9)[a]	6 (27)	14 (64)	22
Doxycycline, 200mg on day 1 of study, and 200mg on day 7 of study	2 (9)	1 (5)[b]	5 (24)[b]	15 (71)[b]	23[b]
Oxytetracycline, 2g daily on days 1-7 of study	0	1 (4)	2 (9)	20 (87)	23
All Subjects	2 (3)	4 (6)[b]	13 (20)[b]	49 (74)[b]	68

[a]numbers enclosed in parentheses are percentages.

[b]primary treatment failures were excluded from the total before frequencies were calculated.

Four patients, 2 in Group DXY I, 1 in Group DXY II and 1 in Group OXY, were treated for recurrent illness (Table 2). These were considered relapses. Patient 171 (Group DXY II) developed a return of fever greater than 39 C on day 5 and 6. He was treated with oxytetracycline beginning on day 6 and was promptly cured. Patient 190 (Group DXY I) responded well to treatment and was afebrile on day 3. Fever returned on day 10 and rickettsiae were isolated from a blood specimen collected on day 11. Oxytetracycline was given on days 17 through 24 with slow subsidence of temperature to a range of 37-37.6 C. Subsequent intermittent low-grade fever persisted for several weeks. This was thought to be associated with a urinary tract infection but a diagnosis was not clearly established. Patient 139 (Group DXY I) was also enigmatic. He was afebrile within 40 hrs of receiving the first drug dose, but experienced a relapse of fever and mild symptoms during the second week. He responded slowly and only partially to retreatment with oxytetracycline. Further returns of fever in subsequent weeks, during which the patient appeared otherwise well, did not seem to be affected by two courses of oxytetracycline and one course of doxycycline. Repeated blood cultures for rickettsiae were negative as were results of standard investigations for fevers of unknown origin. The patient was discharged on the 20th week and was well when examined 3 months later. Patient 151 (Group OXY) experienced temperature elevations on days 7, 9, and 12 which remitted spontaneously; fever returned on days 18 and 19 which was successfully retreated with a second course of oxytetracycline.

All 4 patients who were thought to have had relapses received initial treatment within 4 days after onset of illness (Table 3). Excluding the 2 patients who vomited their initial dose of drug, 62 of 66 (94%) were cured following the protocol treatment alone (Table 4), experiencing rapid initial disappearance of symptoms, usually within 3-5 days. Thirteen (20%) patients experienced elevations of temperature to 37.6 C or greater on 2 or more days during the second and third week of treatment (Table 1). These self-limiting fevers may have represented mild recurrences of rickettsial illness. Temperature elevations of this sort occurred in 6 patients in Group DXY I, 5 patients in Group DXY II and 2 patients in Group OXY. Although these fevers were generally mild and of short duration, sometimes only a single spike of fever on 2 days, they occasionally reached 39 C and in three instances persisted for more than 2 days before spontaneous remission. Associated symptoms were minor or absent and patients were often unaware of fever and denied feeling of ill health. Rashes and eschars were not exacerbated. The frequency of uncomplicated cure was higher in Group OXY than in Groups DXY I and DXY II (Table 5). The difference approached statistical significance ($p=0.0666$).

TABLE 2. Frequency of Relapse among Scrub Typhus Patients by Treatment Group

Treatment group	No. relapses / No. treated	(%)
Doxycycline, single dose (200 mg)	2/22	(9)
Doxycycline, 200 mg on day 1 of study and 200 mg on day 7 of study	1/21[a]	(5)
Oxytetracycline, 2g daily on days 1-7 of study	1/23	(4)

[a]Primary treatment failures excluded.

Hypothesis: Frequency of relapse among those treated with doxycycline was greater than among those treated with oxytetracycline. Not statistically significant, P=0.89 by Fisher's exact test.

TABLE 3. Frequency of Relapse among Patients by Duration after Onset when Treatment Was Begun

Days after onset of symptoms	No. relapses / No. treated[a]	(%)
less than 5	4/30	(13)
5 or more	0/36	

[a]Primary treatment failures excluded.

Hypothesis: Frequency of relapse among patients treated early in their illnesses was greater than among those treated later in illness. Statistically significant difference, P=0.038 by Fisher's exact test.

TABLE 4. Frequency of Subjects Cured without Retreatment by Treatment Group

Treatment group	No. requiring no further treatment / No. treated	(%)
Doxycycline, single dose (200 mg)	20/22	(91)
Doxycycline, 200 mg on day 1 of study and 200 mg on day 7 of study	20/21[a]	(95)
Oxytetracycline, 2g daily on days 1-7 of study	22/23	(96)

[a]Primary treatment failure excluded.

Hypothesis: Oxytetracycline resulted in a higher frequency of cures which did not require further treatment. Not statistically significant, P=0.829 by Fisher's exact test.

TABLE 5. Frequency of Uncomplicated Cure by Treatment Group

Treatment group	No. with uncomplicated cure / No. treated	(%)
Doxycycline single dose (200 mg)	14/22	(64)
Doxycycline, 200 mg on day 1 of study and 200 mg on day 7 of study	15/21[a]	(71)
Oxytetracycline, 2g daily on days 1-7 of study	20/23	(87)

[a]Primary treatment failure excluded.

Hypothesis: Oxytetracycline resulted in a higher frequency of uncomplicated cure than doxycycline. Nearly statistically significant P=0.0666 by Fisher's exact test.

IV. DISCUSSSION

Scrub typhus affected thousands of military personnel who were exposed in the Far East and southwest Pacific during World War II (5). The case fatality ratio observed before specific antibiotic therapy was available ranged from 1% to 30% and full convalescence often took 2 or more months (5,6). Scrub typhus was one of the first rickettsial infections found treatable with chloramphenicol and tetracycline (14). Chloramphenicol and tetracycline have been the drugs of choice for treating scrub typhus and their use has reduced mortality and morbidity. Because antibiotics of choice are rickettsiostatic, host immunity is important in achieving cure (15). Persons who were treated early in the course of their disease were likely to experience relapse unless follow-up doses of antibiotics were administered during convalescence (3,16). Relapses of this sort were common among U.S. military personnel treated in the Vietnam conflict whether or not they received follow-up antibiotics (16). A recent study (9) has shown that single doses of doxycycline can be highly effective for treatment of scrub typhus patients in Malaysia.

In contrast to a study conducted in Malaysia (9), our study a) followed patients in hospital for 3 full weeks instead of one week, b) included 30 patients whose onsets had occurred less than 5 days before treatment was commenced, c) was a double-blind trial, and d) dealt with patients who were drawn from a population from outside the endemic area who had not had lifelong exposure to R. tsutsugamushi infection.

To what degree these differences may account for the contrasting findings of the two trials is not known. Only one of the 4 patients who experienced relapse in our study would have been identified if we had discharged the patients after 7 days. The follow-up procedure used in the Malaysian trial required an outpatient visit on days 10 and 14 and would probably have identified 3 of 4 relapses in our trial.

The Malaysian study (9) included at least one patient with duration of illness as short as 4 days, but the mean duration of illness of Malaysian patients at time of treatment was 10.6 days compared to 5.4 days in our series. The low incidence of eschar and rash and the fact that scrub typhus is a common cause of febrile illness in Malaysia (9) leads us to speculate that patients in the Malaysian trial may have had previous infections with one or more strains of R. tsutsugamushi. This may have caused the Malaysian patients to be less ill and incubate disease longer before the sought treatment.

Our results agree closely with the major finding of Brown et al. (9), in that doxycycline in single doses was highly effective in treating persons acutely ill with scrub typhus.

Doxycycline administered in one or 2 doses cured 40 of 43 (Table 4) patients who retained their medication. The two patients who vomited their initial dose of doxycycline exemplify a concern for single dose therapy. The patient who vomits his initial dose of standard tetracycline or chloramphenicol treatment receives another dose 6 hrs later. The patient on a single dose regimen is without the benefit of additional antibiotic.

It is extremely important to note that some of the patients treated in early stages of acute illness (less than 5 days after onset) experienced relapse of symptoms regardless of whether they received doxycycline or tetracycline. In our series, 4 of 30 (13%) persons beginning treatments less than 5 days after onset experienced relapses. Further, 13 of 66 (20%) patients experienced minor returns of fever which did not require retreatment with antibiotics.

In conclusion, we recommend doxycycline therapy for scrub typhus under difficult field conditions where medical support is limited and drug compliance uncertain. The treatment of acutely ill patients early in their disease involves significant risk of relapse and must include appropriate follow-up procedures to identify and retreat patients who experience return of symptoms.

V. SUMMARY

During 1976 a scrub typhus treatment trial was conducted in the Pescadores Islands of Taiwan. Sixty-eight Chinese military patients with scrub typhus confirmed by recovering R. tsutsugamushi from acute phase blood or by demonstrating a diagnostic rise in indirect immunofluorescent antibody from the acute to the convalescent phase were treated with one of three different treatment regimens. Twenty-two patients received a single dose of 200 mg doxycycline by mouth, 23 patients received a single dose of 200 mg doxycycline by mouth on study day 1 and 7, and 23 patients received oxytetracycline by mouth 500 mg every 6 hours for 7 days. Most patients experienced rapid cures; there were, however, two primary treatment failures with doxycycline (both of which were due to vomiting of the initial dose). Four patients had relapse of symptoms severe enough to require retreatment, and 3 of these had received doxycycline. In addition, 13 patients (doxycycline 11; oxytetracycline 2) had returns of fevers of 37.6C or greater on 2 or more days which resolved without antibiotic intervention but might be considered recrudescences of rickettsial illness. The frequency of illness which necessitated retreatment among patients who received antibiotic therapy less than 5 days after

onset of symptoms was 4 of 30 (13%) and among patients whose therapy commenced after 5 or more days post-onset was 0 of 36. These data documented the heightened risk of relapse in scrub typhus when antibiotic therapy is commenced before 5 days of illness. Further, the data document the occurrence of relapse and recrudescence of self-limited fevers in patients treated with doxycycline.

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on study day 1 and 7, and 23 patients received oxytetracycline by mouth 500 mg every 6 hours for 7 days. Most patients experienced rapid cures; there were, however, two primary treatment failures with doxycycline (both of which were due to vomiting of the initial dose). Four patients had relapse of symptoms severe enough to require retreatment, and 3 of these had received doxycycline. In addition, 13 patients (doxycycline 11; oxytetracycline 2) had returns of fevers of 37.6C or greater on 2 or more days which resolved without antibiotic intervention but might be considered recrudescences of rickettsial illness. The frequency of illness which necessitated retreatment among patients who received antibiotic therapy less than 5 days after onset of symptoms was 4 of 30 (13%) and among patients whose therapy commenced after 5 or more days post-onset was 0 of 36. These data documented the heightened risk of relapse in scrub typhus when antibiotic therapy is commenced before 5 days of illness. Further, the data document the occurrence of relapse and recrudescence of self-limited fevers in patients treated with doxycycline.