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ORIGINAL ARTICLE

Intravenous minocycline versus oral doxycycline for the treatment of noncomplicated scrub typhus

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Background: Scrub typhus is an acute febrile disease for which synthetic tetracycline antibiotics are efficacious. However, no clinical studies have compared oral doxycycline with intravenous minocycline for treatment of scrub typhus.
Methods: We conducted a retrospective analysis in patients diagnosed with noncomplicated scrub typhus by serologic or molecular methods from August 2001 to July 2007. We compared the efficacy of intravenous minocycline with oral doxycycline for treatment of noncomplicated scrub typhus in these patients.
Results: Forty seven cases receiving tetracycline antibiotics for the treatment of noncomplicated scrub typhus were included. There was no statistically significant difference for the response rate between the 25 cases receiving intravenous minocycline (96%) and the 22 cases receiving oral doxycycline (91%) ($p = 0.909$). Kaplan-Meier curve with a long-rank test for the time to defervescence showed no statistically significant difference between minocycline therapy (mean 30 hours; range 4—124 hours) and doxycycline therapy (mean 32.4 hours; range 4—144 hours) ($p = 0.860$). After multivariate Cox regression models, the time to defervescence was only affected by Acute Physiology and Chronic Health Evaluation II score (hazard ratio 0.868; $p = 0.016$). Nearly all patients (93.6%) became afebrile within 72 hours after use of tetracycline antibiotics. Prolonged hospitalization (> 7 days) was correlated with the timing to start tetracycline antibiotics after admission.
Conclusion: Both antibiotics have similar efficacy for the treatment of noncomplicated scrub typhus. Nearly all cases responding to both antibiotics became afebrile within 3 days.

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Introduction

Scrub typhus is an acute febrile human disease caused by *Orientia tsutsugamushi* that is transmitted to human by the bite of an infected chigger. It is a common zoonotic disease of rural Asia and western Pacific islands.[1] In Taiwan, the annual number of confirmed cases has increased from 39 cases in 1990 to 462 in 2005[2] because of the improvement of diagnostic facilities, especially in eastern Taiwan where our hospital is located. Clinical manifestations vary from mild fever to multiple organ failure.[3,4]

Tetracycline compounds have been used for treatment worldwide since their commercial introduction in 1953. The development of synthetic antibiotics began with doxycycline in 1967 and was followed by minocycline in 1972.[5] Treatment with any tetracycline antibiotics for scrub typhus typically results in rapid and complete recovery.[6] Oral doxycycline is absorbed with a bioavailability of more than 80%, mainly in the stomach, duodenum, and jejunum. The oral form is more convenient to use than intravenous form but needs 2—3 hours to reach peak concentrations.[7—9] However, no clinical studies have compared the efficacy for the treatment of noncomplicated scrub typhus between oral doxycycline and intravenous minocycline. The present study was undertaken with this aim.

Methods

We performed a retrospective study at Buddhist Tzu Chi General Hospital (Taiwan), a 900-bed tertiary care university hospital and referral center. Hospitalized patients diagnosed with scrub typhus by serologic or molecular methods were enrolled. Patients complicated before tetracycline antibiotics therapy with acute renal or acute respiratory failure were excluded. The definition of acute respiratory failure was based on the sepsis-related organ failure assessment score criteria in which 3 or 4 [PaO_2/FiO_2 (mmHg) < 200] is defined as severe organ failure.[10] Acute renal failure was defined as a rapid 3-fold increase in serum creatinine, decrease in glomerular filtration rate by 75%, or elevation of serum creatine to more than 4 mg/dL according the Risk, Injury, Failure, Loss, End stage classification of acute renal failure published by the Acute Dialysis Quality Initiative group in 2004.[11] Patients' medical data, including demographic characteristics, medical history, medications, laboratory data, and outcome were collected for analysis.

In our hospital, thermometers were used to check body temperature. Fever was defined as a body temperature more than 37.5°C. When a patient's body temperature returned to normal after fever, it was considered as defervescence. Time to defervescence was defined as the duration between the start of tetracycline antibiotic use and the resolution of fever. Calculation of time to defervescence was based on the timing when the vital signs were checked. In the ordinary ward of our hospital, the vital signs were checked every 8, 6, or 4 hours. Fever could be detected before the moment considered as the timing of defervescence and not detected after that moment. When the patient became defervescence after use of tetracycline antibiotics, we considered a response to the antibiotics had occurred.

Orientia tsutsugamushi serologic testing was performed for the presence of IgM and IgG specific antibodies by use of an indirect immunofluorescence assay.[12] The *O tsutsugamushi* antigens (Gilliam, Karp, and Kato strains) used were cultured in L cells.[13] IgM and IgG titers were determined in acute- and convalescent-phase sera serially diluted 2-fold in phosphate-buffered saline (PBS) from an initial 1:40 dilution. The slides were rinsed and washed twice in PBS (pH 7.4)-containing 0.05% Tween 20 (PBST) for 10 minutes. Fluorescein-conjugated goat anti-human IgM and IgG (Zymed, SanFrancisco, CA, USA) was used at the appropriate dilutions as the secondary antibody. After incubation for 30 minutes, the slides were rinsed and washed twice with PBST. The slides were mounted with mounting fluid (Chemicon, San Diego, CA, USA) under coverslips and observed using an ultraviolet epifluorescence microscope (Nikon, Tokyo, Japan). Sera found positive (IgM $>$ 1:80 or a 4-fold increase in IgG titer in convalescent phase) were titrated to the endpoint.

Peripheral blood mononuclear cells were extracted from heparinized human blood samples by Ficoll/Hypaque density-gradient centrifugation. The genomic DNA of *O tsutsugamushi* was extracted by using the QIAamp Blood Mini Kit (QIAGEN, Valencia, CA, USA) following the manufacturer's protocols. *O tsutsugamushi* infection was diagnosed if the tested specimen was positive for the gene encoding the 56-kDa protein by nested polymerase chain reaction (PCR).[14] Target DNA was amplified in a mixture (total volume, 50 μL) containing 1.5 mM $MgCl_2$, 50 mM KCl, 10 mM Tris-HCl (pH 8.3), 0.001% gelatin, 100 μM dNTPs, 0.2 μM primers, 1.25 U of FastStar Taq polymerase (Roche Diagnostics, Mannheim, Germany) and 5 μL of template DNA. The reaction was performed in 40 cycles of 94°C for 30 seconds, 57°C for 30 seconds, and 72°C for 60 seconds in a PTC-100 thermal cycler (MJ Research, Waltham, MA, USA). The final cycle was followed by an extension step at 72°C for 10 minutes. The size of the PCR-amplified products was determined under ultraviolet light following ethidium bromide staining.

SPSS 11.5 for MS Windows (SPSS Inc., Chicago, IL, USA) software was used for the statistical analysis. Pearson's Chi-squared or Fisher's exact test was used to examine nominal data and unpaired Student's *t* test was used for continuous data. All tests were two-sided and a *p* value of 0.05 or less was considered significant. Time to defervescence was compared by Kaplan-Meier survival methods.

Results

Diagnosis of scrub typhus was confirmed by serology or molecular methods from August 2001 to July 2007 in 62 patients treated by tetracycline antibiotics. Of these, one patient received minocycline and levofloxacin simultaneously, and seven patients received oral minocycline. They were excluded from this study. Seven of the remaining 54 patients had acute renal or acute respiratory failure before usage of tetracycline antibiotics and were excluded. The remaining 47 patients were included for this study. Twenty-five cases received intravenous minocycline (Lederle parenterals, Carolina, USA) and 22 cases received oral doxycycline (China Chemical & Pharmaceutical, Taipei, Taiwan). In the 25