Azithromycin Activities against Orientia tsutsugamushi Strains Isolated in Cases of Scrub Typhus in Northern Thailand

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Azithromycin was given to mice and humans infected with strains of Orientia tsutsugamushi from northern Thailand, where drug-resistant scrub typhus occurs. Azithromycin and doxycycline yielded comparable mouse survival rates (73 and 79%, respectively; P > 0.5). Symptoms, signs, and fever in two pregnant women abated rapidly with azithromycin. Prospective human trials are needed.

More than one billion people in areas of endemcity and travelers are at risk from scrub typhus (8, 9, 12, 13). Macrolide antibiotics have been used to successfully treat drug-sensitive scrub typhus (2, 5) and represent one of the few potential therapeutic options for pregnant women and children infected with Orientia tsutsugamushi, the etiologic agent of scrub typhus. Azithromycin was effective against both doxycycline-sensitive and doxycycline-resistant strains of scrub typhus in vitro (10). Here, we report the activity of azithromycin against strains of O. tsutsugamushi acquired in Chiangrai, in northern Thailand, where drug-resistant strains occur (13).

The susceptibilities of three Chiangrai isolates and of the prototype Karp strain of O. tsutsugamushi to azithromycin and doxycycline were evaluated in mice by methods previously described (13). An intraperitoneal injection of 1,000 50% minimum lethal dose units was given on day 0, and the antibiotics (18 mg/kg/day for doxycycline (4) and 50 mg/kg/day for azithromycin) were administered intraperitoneally, divided into three doses, on days 5 to 8. A higher dose of azithromycin (100 mg/kg/day) was also tested. There were eight female ICR mice in each treatment group; controls were three mice given antibiotic but no organisms and five mice infected but given injections of normal saline rather than antibiotics. The numbers of animals surviving until day 30 in each treatment group were compared by the Mann-Whitney U test. Mice given only antibiotic but no organisms and five mice infected but given injections of normal saline died. The 24 mice infected with the Karp strain survived when treated with either doxycycline or azithromycin (Table 1). There were no significant differences between treatment groups in the numbers of mice surviving infection by the three Chiangrai strains (19 of 24 for doxycycline, 17 of 24 for 50-mg/kg azithromycin, and 18 of 24 for 100-mg/kg azithromycin [P > 0.5]).

This research was conducted in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, NIH publication 86-23 1985 (5a).

Two pregnant women were referred to one of us (P.K.) for management of acute scrub typhus, since both chloramphenicol and doxycycline are best avoided during pregnancy. Patients were treated at the Chiangrai Regional Hospital, a tertiary care referral center in Chiangrai, Thailand. O. tsutsugamushi infection was diagnosed if an immunoblot dipstick test (Dip-s-Ticks; Integrated Diagnostics, Baltimore, Md.) was positive (4) or if the indirect immunoperoxidase assay showed immunoglobulin M titers that were ≥1:400 and/or immunoglobulin G titers that were ≥1:1,600 (14). Oral azithromycin was administered in a 500-mg dose on the first day, followed by 250 mg daily on days 2 to 5. Temperature was measured orally every 8 h; the fever clearance time was the interval between the first dose of azithromycin and the time at which the patient’s fever fell to and remained at or below 37.2°C without an antipyretic.

The first patient was a 26-year-old rice farmer with two prior spontaneous abortions who presented with fever, cough, and hearing loss that had lasted for 3 days accompanied by generalized lymphadenopathy. The last menstrual period had begun 20 days prior to admission, and a urine pregnancy test was positive. Symptoms resolved rapidly after azithromycin treatment was begun; the fever clearance time was 51 h. An episode of transient abdominal pain accompanied by vaginal bleeding occurred on the third hospital day. The patient was discharged upon completion of the course of azithromycin and was afebrile, asymptomatic, and working again when seen at a follow-up visit 3 weeks later. A urine pregnancy test conducted during this visit was negative.

The second patient was a 30-year-old rice and corn farmer who presented with fever that had lasted for 10 days accompanied by cough, hearing loss, lymphadenopathy, and conjunctival suffusion. Ultrasound showed a healthy fetus, with the gestational age estimated to be 26 weeks. The patient’s fever resolved 36 h after the first dose of azithromycin, and she was afebrile and asymptomatic when discharged from the hospital after the final dose of azithromycin. She had neither symptoms nor fever at a follow-up visit 5 days after leaving the hospital. However, she did not return for the next scheduled follow-up appointment and the outcome of her pregnancy is not known.

The treatment of pregnant women and children infected with O. tsutsugamushi poses several problems. Chloramphenicol is best avoided during pregnancy and cannot be given to neonates; tetracycline is contraindicated in pregnancy because of its teratogenic potential, and repeated long courses administered to young children cause staining of the permanent teeth. The need for a safe, effective treatment for pregnant women and infants is underscored by recent documentation of the transmission of scrub typhus from mother to fetus (11).
Azithromycin has demonstrated no mutagenic potential in standard laboratory tests and in animals; i.e., no teratogenic or adverse reproductive effects have been noted, a result that is consistent with the current classification of the drug in pregnancy category B (6). Macrolides are considered safer than other antibiotics for use in young children and pregnant women and could be of great practical benefit for treatment of *O. tsutsugamushi* infection during pregnancy and early childhood (2,7). The first patient probably had a spontaneous abortion on the third hospital day. However, it is unlikely that azithromycin was responsible, since no adverse reproductive effects have been reported with its use. This individual had had two previous spontaneous abortions, the most recent of which had occurred only six months prior to her scrub typhus infection. Abortion is common in untreated rickettsial disease (15), and symptoms resolved promptly after azithromycin treatment was begun in both patients. Azithromycin was no more effective than doxycycline in mice infected with strains of *O. tsutsugamushi* from northern Thailand, although only 24 mice received each antibiotic (Table 1). Additional results with 192 infected mice confirm that azithromycin and doxycycline have comparable effects against Chiangrai strains (15). Antibiotics with more potent action against resistant scrub typhus are needed. Meanwhile, however, azithromycin could be tried as a last resort in patients in whom standard antibiotics have failed. Azithromycin can prevent malaria (1) and could be of use in the chemoprophylaxis of scrub typhus. Prospective clinical trials are now needed to evaluate the efficacy of azithromycin for the prevention and treatment of scrub typhus.

## REFERENCES


15. Watt, G. Unpublished data.