

AZITHROMYCIN-QUININE COMBINATION THERAPY FOR THE TREATMENT OF UNCOMPLICATED *FALCIPARUM* MALARIA IN THAILAND

Miller RS, McDaniel P, Wongsrichanalai C, Buathong N, Thanosingha N, Walsh DS, Knirsch C and Ohrt C

Azithromycin displays the most potent antimalarial activity among the current macrolide antibiotics, and has a proven safety record in children and pregnant women. Furthermore, it has shown synergy with chloroquine and quinine *in vitro*. Oral quinine administered for 7 days remains a second-line antimalarial regimen in combination with tetracyclines in SE Asia, and is standard of care as a single agent for treatment of *falciparum* malaria in pregnancy. We tested combinations of azithromycin and quinine for the treatment of uncomplicated multi-drug resistant *falciparum* malaria at the inpatient research unit of the AFRIMS-Kwai River Clinical Center along the Thai-Myanmar border. Four regimens were assessed in a dose ranging format (n=10), and fully efficacious doses confirmed in an additional 10 volunteers. The doses consisted of oral quinine (30 mg/kg/d divided q8h) with oral azithromycin (500 mg BID for 3 days; 500 mg BID for 5 days; and 500 mg TID for 3 days). Quinine and doxycycline (100 mg BID) for 7 days served as a control. Cinchonism occurred in all subjects without requiring discontinuation of therapy; however, the azithromycin regimens all had fewer side effects than the doxycycline-quinine combinations. No severe adverse effects were observed. Treatment was given under observation, and volunteers were followed for 28 days in hospital to prevent further malaria transmission. Seven days of quinine-doxycycline cured 100% of volunteers. The azithromycin-quinine combinations showed a dose response effect with both regimens with >4.5 grams of azithromycin (500 mg BID for 5 days and 500 mg TID for 3 days) leading to cure despite shorter treatment durations. The lower dose with 3 grams of azithromycin revealed one (10%) recrudescence at day 28. Three-day azithromycin-quinine combination therapy appears safe and effective. It warrants further evaluation as an effective short course quinine combination with potential for additional use in pediatric and obstetric populations.

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