

cases of RIII were also highly mefloquine resistant, a drug that is widely used in Thailand and that is known for its cross-resistance with quinine.

In conclusion, these preliminary data suggest that azithromycin-artesunate, even when given only once daily for 3 days, as well as azithromycin-quinine TID may be safe and highly efficacious combination treatments for uncomplicated falciparum malaria.

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COMPARATIVE EFFICACY OF INTRAVENOUS ARTESUNATE AND ARTELINATE IN AN UNCOMPLICATED MODEL AND SEVERE PRIMATE MALARIA MODEL

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Plasmodium coatneyi is a primate malaria whose schizonts sequester in the tissues of the lung, heart and brain, mimicking *Plasmodium falciparum* infection. Using a severe malaria model of *P. coatneyi* in splenectomized rhesus, we found that parasitemias reach high densities ($> 1,000,000/\mu\text{l}$) and the infection is uniformly fatal, if untreated. We validated a treatment window for rescue with parenteral antimalarials using quinine, and here we report comparison of efficacy testing with the two candidate intravenous artemisinin, sodium artesunate (AS) and artelinate lysine salt (AL). Animals were randomized to receive artesunate and artelinate by IV bolus injection for 3 days, in dose-escalation cohorts targeted to achieve 100% parasite clearance. 5 animals received quinine intramuscularly with 20% mortality, and mean parasite clearance time of 5.6 days. Artesunate (4, 6 or 8 mg/kg) was associated with an 11% mortality, and rapid parasite reduction ($> 99.99\%$) with complete parasite clearance in 66%, 50% and 100% of animals, respectively. All animals had recur-descence (mean 4.5 days). Equimolar doses of artelinate (5.9, 8.8 and 11.8 mg/kg) also resulted in a rapid, 4-log reduction in parasitemia, but no animals successfully cleared their parasitemia. Higher doses (23.6 and 47 mg/kg) were associated with increased mortality, despite no life-threatening toxicities noted in healthy rhesus at these doses. The most effective doses (8 mg/kg AS; 11.8 mg/kg AL) were tested in a cohort of monkeys with uncomplicated *P. coatneyi* infection. All AS-treated animals cleared with eventual recur-descence (mean 6 days). Only 2 of 8 AL-treated animals cleared parasitemia with recur-descence within 1-2 days. Unexpectedly, three AL-treated animals developed a shock-like syndrome after treatment, with no clear etiology. In summary, while both drugs rapidly cleared parasitemia, artesunate was more effective in both the severe and uncomplicated models. In view of this and other studies, artesunate has been chosen for advanced clinical development.

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