

ARTEMETHER BIOAVAILABILITY AFTER ORAL OR INTRAMUSCULAR ADMINISTRATION IN UNCOMPLICATED FALCIPARUM MALARIA

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The antimalarial activity of artemether following oral or intramuscular administration in the plasma of 15 adults with acute uncomplicated *Plasmodium falciparum* malaria was measured by bioassay. The peak concentrations in plasma following oral administration were higher in patients with acute illness (median, 1,905 mmol of dihydroartemisinin [DHA] equivalents per liter; range, 955 to 3,358 mmol of DHA equivalents per liter) than in patients in the convalescent phase (median, 955 mmol of DHA equivalents per liter; range, 576 to 1,363 mmol of DHA equivalents per liter), and clearance (CL/F) was lower in patients in the acute phase (1.11 liters/kg/h; range, 0.21 to 3.08 liters/kg/h) than in patients in the convalescent phase (median, 2.76 liters/kg/h; range, 1.56 to 5.74 liters/kg/h) ($P \leq 0.008$). Antimalarial activity in terms of the peak concentration in plasma (C_{max}) after oral administration was a median of 16 times higher than that after intramuscular administration. The ratio of the area under the plasma concentration-time curve during the first 24 h (AUC_{0-24}) after oral administration of artemether to the AUC_{0-24} after intramuscular administration was a median of 3.3 (range, 1 to 11) ($P=0.0001$). In the acute phase, the time to C_{max} was significantly shorter after oral administration (median, 1 h; range, 0.5 to 3.0 h) than after intramuscular administration (median, 8 h; range, 4 to 24 h) ($P=0.001$). Intramuscular artemether is absorbed very slowly in patients with acute malaria.

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ASSESSMENT OF THE NEUROTOXICITY OF ORAL DIHYDROARTEMISININ IN MICE

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High doses of the oil soluble antimalarial artemisinin derivatives artemether and arteether given by intramuscular injection to experimental mammals produce an unusual pattern of selective damage to brain stem centres predominantly involved in auditory processing and vestibular reflexes. We have shown recently, in adult Swiss albino mice, that constant exposure either from depot intramuscular injection of oil-based drug, or constant oral intake carries relatively greater neurotoxic potential than other methods of drug administration. Using the same model, oral dihydroartemisinin was administered once daily at different doses ranging from 25-300 mg/kg/day for 28 days. The neurotoxic potential of the oral dihydroartemisinin was assessed and compared to the oral artemether and artesunate. Oral artemether, artesunate, and dihydroartemisinin had similar neurotoxic effects with no significant toxicity at doses below 200mg/kg/day. These data indicate that once and twice daily oral administration of

artemether, artesunate and dihydroartemisinin is relatively safe when compared to intramuscular administration of the oil based compounds.

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

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Plasmodium coatneyi is a primate malaria whose schizonts sequester in the tissues of the lung, heart and brain, mimicking *P. falciparum* infection. Using a severe malaria model of *P. coatneyi* in splenectomized rhesus, we found that parasitemias reach high densities ($> 1,000,000/(m)l$) 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 recrudescence (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 recrudescence (mean 6 days). Only 2 of 8 AL-treated animals cleared parasitemia with recrudescence 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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