

PHARMACOKINETICS/PHARMACODYNAMICS OF INTRAVENOUS ARTESUNATE AND ARTELINATE USING A *PLASMODIUM COATNEYI*-RHESUS MONKEY MODEL OF SEVERE MALARIA

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Plasmodium falciparum malaria is the cause of 1 to 1.3 million deaths each year. The mortality is mostly due to severe malaria. *P. coatneyi* is a sequestering primate malaria and in a splenectomized animal produces a model to assess drug response to severe malaria. Methods: Equimolar dose of parenteral artesunate (8 mg/kg) and artelinate (11.8 mg/kg), the new artemisinin derivative, were intravenously administered to 10 *rhesus* monkeys when healthy and then again when infected with *P. coatneyi*. Consequently, each monkey served as its own control of intra-subject variation. The treatment was initiated at parasitemia 3 to 14 % or > 200,000 parasites/microL when animals were minimally symptomatic. Blood was collected at 0, 5, 20, 40 min, 1, 3, and 6 h post-dose and plasma samples were divided for simultaneous measurement by HPLC and bioassay. The plasma levels of parent drug and its primary metabolite were measured by HPLC with electrochemical detection (reductive mode). The total antimalarial activity of the drug and all active metabolite(s) in plasma were measured by bioassay against *P. falciparum* (W2 clone). Results: The antimalarial activity of artesunate is contributed by both parent drug and its active metabolite, dihydroartemisinin (DHA), until 20 min post-dose, when only DHA remains in the plasma. On the other hand, artelinate seems to be responsible for all the antimalarial activity in plasma (healthy rhesus, n = 3), even though 2-hydroxyartelinic acid, an active metabolite, is detected by HPLC. Furthermore, no DHA is found in all the plasma from either healthy or infected monkeys. The pharmacokinetic/pharmacodynamic comparison between I.V. artesunate and artelinate in healthy versus malaria infected states will be presented.

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