

***PLASMODIUM COATNEYI* - RHESUS MONKEY MODEL FOR EFFICACY DRUG STUDIES OF INTRAVENOUS ARTEMISININ DERIVATIVES**

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A major impetus for development of intravenous artemisinins is reduction in the morbidity and mortality of severe malaria. *Plasmodium coatneyi* is a sequestering primate malaria that leads to death in splenectomized *rhesus* monkeys from overwhelming parasitemia and sequestration in multiple organs, including the brain. We have adapted this model for testing efficacy of rapid acting antimalarial compounds. After injection of 5×10^4 parasites from an infected spleen-intact donor, parasitemia rises in a tertian pattern, achieving sufficient parasitemia to produce observable symptoms on day 6-8 after injection. Study of efficacy in uncomplicated malaria can be performed in this time frame with parasitemias in the 3-14% range. Parasitemia will rise dramatically with the next schizogony, achieving parasitemias between 35-55% ($>1,000,000$ parasites/ml) and marked clinical illness manifested by high fevers, lethargy, marked anorexia and occasional vomiting, marked anemia, jaundice, epistaxis and hemoglobinuria leading to renal failure. Untreated, mortality is likely within 24-48 hours. We developed criteria for a "treatment window" in which to initiate intravenous artemisinin therapy at the onset of these severe malaria symptoms. Criteria include any of the following: severe lethargy, severe anorexia, new onset jaundice, severe anemia (Hgb ≤ 8 mg/dl) or parasitemia $\geq 25\%$. Using these criteria, initiation of intramuscular quinine (n=5) routinely resulted in rescue from impending death in all but one animal. Time to clearance of parasitemia was 124 hours, with resolution of severe clinical symptoms in about 3 days. Intravenous artesunate (Guilin) was administered daily for 3 days with an initial loading dose. Among the higher dose groups (4mg/kg, 6mg/kg and 8 mg/kg), 8 of 9 animals fully recovered despite initial critical illness. While the model has a major limitation of very rapid escalation of parasitemia and corresponding clinical signs, and hence a narrow window for therapeutic intervention, it appears to serve well to test drugs designed for treatment of severe malaria.

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