A novel endothelin receptor antagonist increases rates of cerebral malaria survival

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Background: Cerebral malaria (CM) in humans is the most severe neurological complication of *Plasmodium falciparum* infection, leading to encephalopathy as well as high rates of mortality in developing countries. Previously, we demonstrated that infection of C57BL/6 mice with *Plasmodium berghei* ANKA (PbA) was associated with cerebral vasculopathy, which resulted in a significant reduction in cerebral blood flow, neuronal dysfunction, axonal injury and impaired metabolic function. These abnormalities were associated with neurological and behavioral deficits in CM mice both during acute infection and after successful resolution of infection with antimalarial therapy. The role of endothelin-1 (ET-1) in the brain is increasingly recognized as a contributor to the pathogenesis of CM. Our studies demonstrated that the endothelin pathway is associated with vasculopathy, neuronal injury and inflammation in CM. Therefore, the components of the ET-1 pathway may be important targets for adjunctive therapy in CM, and may help in preventing neuronal damage during malaria infection.

Hypothesis: We hypothesized that the components of the ET-1 pathway are important targets for adjunctive therapy in CM, preventing neuronal damage during malaria infection.

Methods: PbA-infected (CM) mice (n=10), weighing approximately 20 g, were treated with 1,3,6-trisubstituted-2-carboxy-quinol-4-one**,** a novel ET_A receptor antagonist synthesized by our group. A control group (n=10) was treated with vehicle. The compound was administered via intraperitoneal injection, at 50 mg/kg, once a day for ten days, beginning one week after infection. Mice were followed for changes in weight and serum glucose levels and length of survival.

Results and Discussion: Treatment with 1,3,6-trisubstituted-2-carboxy-quinol-4-one improved all measures of well-being in PbA-infected CM mice, including rates of survival ($p<0.05$). These results were obtained even in the absence of treatment with antimalarials. These findings are consistent with the results from our previous study utilizing a non-selective ET_A/ET_B antagonist. The data presented suggest that our novel ET_A receptor antagonist may ameliorate the alterations in the vasculature which lead to inflammation, neurological dysfunction and subsequent death in mice with CM.

Conclusion: A novel synthetic endothelin A receptor antagonist, 1,3,6-trisubstituted-2-carboxy-quinol-4-one, increases rates of survival in the setting of cerebral malaria in a murine model. ET-1 receptor antagonists may represent important adjunctive therapy in CM.