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## **Plasmodium berghei: efficacy of 5-fluoroorotate in combination with commonly used antimalarial drugs in a mouse model.**

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**Abstract**

Resistance to antimalarial antifolates necessitates a search for new antimetabolites targeting other enzymes of the folate metabolic pathway. In this study, 5-fluoroorotate (FOA), reported to be an inhibitor of thymidylate synthase, was assayed against *Plasmodium berghei* NK 65 in mice, with(out) an oral uridine supplement. FOA (2.5 and 5.0 mg/kg bw.) was tested alone, or in a double and triple combination with a fixed oral dose of 1.25 and 2.5 mg/kg of pyrimethamine (PYR); 1.0 and 2.0 mg/kg of dapsone (DAP); 1.0 and 2.0 mg/kg of artesunate (ART). FOA achieved high suppression which ranged from 95.7% to aparasitaemic, activity that was dose-dependent. At the highest dosages used, FOA-PYR and FOA-DAP-ART combinations were synergistic with 100% cure rate, while FOA-PYR-ART was antagonistic. Drugs in a synergistic combination may exert less resistance selection pressure, thus FOA-PYR and FOA-DAP-ART warrant further evaluation with an ultimate object of possible clinical use against drug-resistant malaria.

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