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A combination of tetrandrine and chloroquine effectively treats chloroquine resistant Falciparum malaria (human) in *Aotus* monkeys

Knox Van Dyke
West Virginia Medical School, USA

The drug resistance to chloroquine(CQ) which has now spread through most of the tropical world in the last 50 years has greatly decreased the effectiveness of the gold standard of anti-malarial drugs thus creating a constant new search for new and effective anti-malarials. Our early in vitro studies (1989) using chloroquine sensitive (CS) and chloroquine resistant strains first revealed that tetrandrine (TT) had important anti-malarial activity against both malarial strains of P. falciparum infecting human erythrocytes. When low doses (1-3 micromolar range) of tetrandrine were combined with (0.1-0.3 micromolar range) of chloroquine a surprising 43 fold synergism occurred using Berenbaum plots. Possibly a synergistic combination of antimalarials might be curative in humans. Therefore, a malarial-infected Aotus monkeys were used to test the idea. Briefly, the Vietnam Smith strain of chloroquine- resistant falciparum malaria was inoculated into Aotus monkeys. Oral drug treatment with CQ was with 20 mg/kg and given with various doses of tetrandrine from 15mg/kg to 60 mg/kg depending on experimental conditions. Parasitemia was rapidly cleared with CQ and TT but CQ alone was ineffective. Recrudescence occurred within 7 day post infection. A second treatment cured the animals of malaria. Responses were likely due to a combination of the drugs and host immune response. An infected animal treated with CQ eventually died. The combination of TT and CQ forms the basis of a new attack on CQ resistant malaria. The TT inhibits multiple drug resistance (MDR) and MDR-ATPase. It likely acts against PfCRT the chloroquine resistance transporter using a mechanism similar to verapamil but without the toxicity.

Biography

Knox Van Dyke obtained his Ph.D. at Saint Louis University in the Nobel prize winning Department of Biochemistry In 1966. He did postdoctoral studies at West Virginia University-Department of Pharmacology working on the development of a new screening system for anti-malarial drugs. This method or variations of it have been used around the world for almost 50 years. He has concentrated on defeating drug resistance in malaria, cancer and many other diseases. He has over 300 publications, multiple books and multiple chapters.

kvandyke@hsc.wvu.edu