

COMPARATIVE SUBACUTE TOXICITY OF INTRAVENOUS ARTESUNATE AND ARTELINATE IN THE RHESUS MONKEY

Van Gessel YA, Miller RS, Gettayacamin M, Hansukjariya P, Petras JM, Ithiweerakul M, Teja-Isavadharm P, Weina PJ and Blanchard TW

A comparison of the subacute toxicity of the two leading intravenous artemisinin formulations, sodium artesunate (AS) and artelinate lysine (AL) salt, was performed in rhesus monkeys. Maximum tolerated dose for AS and AL was determined using an escalating single dose study. Based on these results a 7-day subacute toxicology study was designed with four AL groups (vehicle control, 5.9 mg/kg, 11.8 mg/kg and 47.2 mg/kg) and six AS groups (vehicle control, 4 mg/kg, 8 mg/kg, 16 mg/kg, 32 mg/kg and 128 mg/kg). Test compound was administered once daily for 7 consecutive days as a rapid intravenous injection. Animals were humanely euthanized 14 days after completion of drug therapy and a complete necropsy was performed. Additional study parameters included clinical observations, food intake, body weight, routine serum chemistry, urinalysis and complete blood count with reticulocyte count. Results showed that the drugs had different toxicity patterns with dose-related toxicities. AS was most associated with reversible reticulocytopenia and leucopenia, and thrombocytopenia at high doses. Diarrhea developed at 16 mg/kg or greater by the end of treatment and resolved about a week after completion of dosing. Highest doses (128 mg/kg) were associated with vomiting and severe, bloody diarrhea. Liver and renal functions were minimally affected. AL caused no diarrhea and modest reticulocytopenia. However, moderately elevated liver function tests and creatinine were noted, and hemolysis and hemoglobinuria were seen more frequently than at equimolar doses of AS. The no adverse effect levels were 4 mg/kg and 11.8 mg/kg for AS and AL, respectively. Both drugs caused transient drooling, reduced motor activity and balance disturbances at doses greater than 32 mg/kg, and AL caused marked sedation at higher doses. Only rare clinical neurologic disturbances were noted 2 hours after any treatment, and the brainstem neuropathologic lesions seen with oil-soluble artemisinin derivatives were not present at the time point examined. Overall AS was judged to be less toxic than AL.

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EFFICACY OF MONTHLY TAFENOQUINE FOR PROPHYLAXIS OF *PLASMODIUM VIVAX* AND MULTIDRUG-RESISTANT *P. FALCIPARUM* MALARIA

Walsh DS, Eamsila C, Sasiprapha T, Sangkharomya S, Khaewsathien P, Supakalin P, Tang DB, Jarasrumsichol P, Cherdchu C, Edstein MD, Rieckmann KH and Brewer TG

We assessed monthly doses of tafenoquine for preventing *Plasmodium vivax* and multidrug-resistant *P. falciparum* malaria. In a randomized, double-blind, placebo-controlled study, 205 Thai soldiers received either a loading dose of tafenoquine 400 mg (base) daily for 3 days, followed by single monthly 400-mg doses ($n = 104$), or placebo ($n = 101$), for up to 5 consecutive months. In volunteers completing follow-up (96 tafenoquine and 91 placebo recipients), there were 22

P. vivax, 8 *P. falciparum*, and 1 mixed infection. All infections except 1 *P. vivax* occurred in placebo recipients, giving tafenoquine a protective efficacy of 97% for all malaria (95% confidence interval [CI], 82%-99%), 96% for *P. vivax* malaria (95% CI, 76%-99%), and 100% for *P. falciparum* malaria (95% CI, 60%-100%). Monthly tafenoquine was safe, well tolerated, and highly effective in preventing *P. vivax* and multi-drug-resistant *P. falciparum* malaria in Thai soldiers during 6 months of prophylaxis.

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A HIGHLY SENSITIVE METHOD FOR MEASURING THE RESPONSE OF *PLASMODIUM FALCIPARUM* TO ANTIMALARIALS

Krairojananan P, Jones JW, Russell BM, Barends M and Khuntirat B

Real time quantitative PCR (rtqPCR) is the most sensitive method for determining the quantity of malaria parasites in a sample. RtqPCR (cybergreen) has successfully applied to determine *Plasmodium falciparum* sensitivity to chloroquine, as reported previously. We have developed an optimized rtqPCR drug assay utilizing an 18S rRNA Taq probe set/ABIprism system to determine the sensitivity of *P. falciparum* to antimalarials. By comparing the copy number of the 18S rRNA gene of parasites grown in the control and drug treatment we were able to provide a direct measurement of parasite growth. In a parallel study, we compared the drug sensitivity data of *P. falciparum* field isolates from Northwest Thailand using rtqPCR, and other methodologies (HRP2 ELISA and *pf*PLDH DELI methods). There was no significant difference in the overall drug response trends shown by the rtqPCR, HRP2 ELISA and *pf*PLDH DELI methods. However, these current methodologies for *in vitro* drug sensitivity testing are indirect methods with poor sensitivity and limited to screening profile and have significant shortcomings, which may lead to inaccurate and potentially dangerous data on drug efficacy. We are confident that the rtqPCR technique is a sound candidate for use as a gold standard not only to measure IC50 of randomly selected isolates and clones (QA), but also to measure the accuracy of the current (Hypoxanthine) and other future drug assays (PicoGreen). (ACMCIP abstract)

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A HISTIDINE-RICH PROTEIN 2-BASED MALARIA DRUG SENSITIVITY ASSAY FOR FIELD USE

Noedl H, Bernhard A, Walther HW, Herwig K and Robert SM

With the spread of antimalarial drug resistance, simple and reliable tools for the assessment of antimalarial drug resistance, particularly in endemic regions and under field conditions, have become more important than ever before. We therefore developed a histidine-rich protein 2