ABSTRACT.

ACCUMULATION OF CHLOROQUINE (CQ) AND AN INVESTIGATIONAL AMINOQUINOLINE (AQ-13) BY CQ-SUSCEPTIBLE AND CQ–RESISTANT Plasmodium falciparum. Haiyan Deng, Simon J. Hocart and Donald J. Krogstad, Departments of Tropical Medicine and Medicine, Center for Infectious Diseases and the Peptide Research Laboratory, Tulane University Health Sciences Center, New Orleans, LA.

In the studies reported here, we compared the accumulation of an investigational AQ active against both CQ-susceptible and -resistant parasites (AQ-13) by CQ-susceptible and –resistant Plasmodium falciparum to the accumulation of CQ (which is active only against CQ-susceptible parasites). Based on the peak blood levels achieved during recent pharmacokinetic (Phase 1) studies in human volunteers, these studies used 3 μM concentrations of AQ-13 and CQ in human plasma with 10% suspensions of red cells (10% Hct) containing 5% synchronous ring stage parasitemias or unparasitized red cells. After incubation for 2 hours at 37⁰ C followed by centrifugation, AQ accumulation was measured by extracting the CQ or AQ-13 from the red cell pellet and plasma, and by quantifying AQ accumulation using fluorescence HPLC. With CQ-susceptible parasites (Haiti 135/CDC strain), there was substantial accumulation of both CQ (mean accumulation of 976 fmols per 10⁶ parasitized red blood cells [PRBCs]) and AQ-13 (5,172 fmols per 10⁶ PRBCs). In contrast, with CQ-resistant parasites (Indochina I/CDC strain), there was readily measurable accumulation of AQ-13 (966 fmols per 10⁶ PRBCs), but not of CQ (-200 fmols per 10⁶ PRBCs). The accumulation of CQ and AQ-13 by the CQ-susceptible Haiti strain is consistent with the activity of both CQ and AQ-13 against CQ-susceptible parasites at low nanomolar concentrations (IC50s 3-5 nM). Conversely, the accumulation of AQ-13 but not CQ, by the CQ-resistant Indochina I strain is consistent with the activity of AQ-13, but not CQ, against those parasites (IC50s 5-10 and > 250 nM, respectively). These results suggest that there is no detectable accumulation of CQ by CQ-resistant P. falciparum parasites at the peak blood concentrations achieved with the standard 1500 mg base therapeutic dose of CQ.