

- 248 EPIDEMIOLOGY OF CHLOROQUINE RESISTANT *PLASMODIUM VIVAX*: OVERVIEW AND BRIEF METANALYSIS. Maris DC\*, Baird JK, and Hoffman SL. Naval Medical Research Institute, Bethesda, MD.

*Plasmodium vivax* is the second most common cause of malaria. Chloroquine has been the drug of choice for both therapy and prophylaxis since 1946. Resistance to chloroquine by *P. vivax* was first confirmed in 1989 from Papua New Guinea. Here we describe a meta-analysis of subsequent case reports and surveys of chloroquine-resistant *P. vivax* conducted in Southeast Asia, Oceania and India. Four distinct methods of detecting the problem are described: 1) case report, 2) survey by chemotherapeutic assessment, 3) survey by chemoprophylactic assessment, and 4) survey by measurement of chloroquine levels at clinical presentation. The available data reveal a patchy distribution of the problem. Resistance has been described by case reports from India, Myanmar, Sumatra Indonesia and Papua New Guinea. Resistance has been confirmed by survey in Myanmar, Irian Jaya, and Sumatra and North Sulawesi, Indonesia. Negative surveys have been reported from Thailand, the Philippines, and the islands of Java and Lombok in Indonesia. Routine failure of supervised chloroquine prophylaxis in carefully controlled trials has been reported from Irian Jaya. Finally, the prevalence of self-administered whole blood chloroquine levels in excess of the minimally effective concentration among patients with slide proven vivax malaria in Irian Jaya is reportedly 96%. The emergence of chloroquine resistant *P. vivax* further complicates the management of malaria in children and pregnant women. Careful monitoring of the spread of chloroquine resistant *P. vivax* will be required in the future.

- 249 METABOLISM OF ARTEETHER (AE): COMPARISON IN MALARIA-INFECTED AND NORMAL RAT IN VITRO MODELS. Leo KU\*, Grace JM, Peggins JO, Aguilar A, and Brewer TG. Walter Reed Army Institute of Research, Division of Experimental Therapeutics, Washington, DC; and Armed Forces Institute of Medical Research, Bangkok, Thailand.

Disease effects on drug metabolism and disposition are important in terms of altered efficacy, toxicity, and drug-drug interactions in patients with malaria. Few data are available detailing the effect of malaria infection on the metabolism of most antimalarial drugs and in particular the artemisinin drugs. We studied the effect of *Plasmodium berghei* malaria infection on metabolism of one artemisinin antimalarial, arteether (AE), using liver microsomes (MICS) and the isolated perfused rat liver (IPRL). Arteether (AE) is primarily deethylated to dihydroquinhaosu (DQHS) in rats and humans. Conversion of AE to DQHS is impaired at all concentrations of AE (0 to 300  $\mu\text{M}$ ) in MICS from malaria-infected rats. The  $K_m$  for AE was 123  $\mu\text{M}$  and 89  $\mu\text{M}$ ;  $V_{max}$  was 1.0 and 0.83 nmol AE formed/mg protein-min in control and infected MICS, respectively. Calculated intrinsic clearance ( $CL_{int} = \text{Initial } V_{max}/K_m$ ) for AE was only 3 % lower in infected microsomes. Apparent pharmacokinetic parameter estimates for AE in perfusate and bile were derived using the IPRL model. There were no differences ( $p > 0.05$ ) in volume of distribution,  $V_d$ , clearance,  $CL$ , and half-life,  $t_{1/2}$  between normal and infected animals. There was a significant ( $p < 0.05$ ) decrement in biliary disposition of  $^{14}\text{C}$ -AE in bile samples from malaria infected rats. Malaria infection significantly decreased the metabolic conversion of arteether to DQHS and biliary disposition of drug label in these models. Apparent pharmacokinetic parameter estimates for AE were not different in malaria infection.

- 250 IN VIVO SUSCEPTIBILITY OF *PLASMODIUM FALCIPARUM* TO CHLOROQUINE AND AMODIAQUINE IN 1 TO 15 YEARS CHILDREN IN SOUTHERN CAMEROON. /Le Hesran JY\*, Boudin C, Personne P, Devries C, Chambon R, Foumane V, Fievet N, and Cot M. Institut Franais de Recherche scientifique pour le développement en Coopération (ORSTOM), Paris, France; Organisation de coordination et de lutte contre les endémies en Afrique Centrale (OCEAC), Yaounde, Cameroon; and University of Nijmegen, The Netherlands.

Since 1985, chloroquine resistance (CR) became evident in Cameroon, and rapidly spread out over the country. Despite such a situation, chloroquine is still the first antimalarial drug. CR follow up was mostly carried out by *in vivo* tests among schoolchildren. In this population, of a mean 9 yrs of age, a CR rate of 30 to 45% was reported. However, this may not show the true level of CR, because of the interaction of immunity in controlling parasite growth. Therefore, in southern Cameroon, we studied the activity of 25 mg/kg over 3 days of chloroquine and amodiaquine in treating asymptomatic children ranging from 1 to 15 yrs, with parasite density  $> 1000/\mu\text{l}$ . Following chloroquine treatment, children with treatment failure by D7 in the 0-2, 3-4, 5-9 and 10-15 yrs age groups were: 26/37 (71%), 9/21 (43%), 24/43 (56%) and 12/30 (40%). Four infections were RIII, all in the 0-2 yrs group. 41 of the 60 children with a D7 negative blood smear were seen again at D14: 19 of these (46%) were positive. Following amodiaquine, children with treatment failure by D7 were: 3/28 (11%), 2/20 (10%), 1/17 (6%) and 0/6. No RIII level was observed. 44 of the 65 children with a D7 negative blood smear were seen on D14: 7 (16%) had a positive blood smear, 5 being in the 0-2 yrs group. The prevalence of CR in southern Cameroon is high, especially in young children. The prevalence and level of CR decreased with age. Amodiaquine is effective  $> 89\%$  in all age groups, and might be considered as a first line treatment in young children. Medical practitioners must be provided with information on resistance within groups having not yet acquired premunition.



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