**COMPARISON OF PHARMACOKINETICS-PHARMACODYNAMICS**

**OF ARTEMISININ DERIVATIVES IN HEALTHY NORMAL**

**VOLUNTEERS AND UNCOMPLICATED MALARIA PATIENTS**

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**ABSTRACT**

The Artemisinin class of compounds is the most rapidly acting of all antimalarials. Two artemisinin derivatives, artemether and artesunate have been most widely used in the treatment of multi-drug resistant falciparum malaria. Artesunate (AS) and most other artemisinin derivatives (artemether, arteether) are biotransformed to dihydroartemisinin (DHA), the major active metabolite. Dihydroartemisinin is the most potent member of the class in *in vitro* test system. It is synthesized by chemical reduction of artemisinin extracted from the Chinese herb and is used as the starting material for the manufacture of artesunate, aitemether, and arteether. Since DHA is the most potent and least expensive to manufacture, it has the potential to be developed as an antimalarial drug in the market.

Aiiesunate is readily biotransformed to dihydroartemisinin and, therefore, measurement of antimalarial activity in blood provides a critical pharmacodynamics endpoint. Quantitative determination of plasma total antimalarial activity can be performed by the use of an *in vitro Plasmodium falciparum* bioassay method, which has been validated to measure drug in serum or plasma samples from patients given artemisinin compounds. The plasma antimalarial activity is reported as the concentration equivalent to DHA. In other words, the antimalarial activity of AS is reported as the concentration of DHA that produces the same antimalarial activity as AS. Data from the bioassay provides information on the pharmacokinetic pharmacodynamic or the effect kinetic profile of the drugs.

As part of the drug development process, the pharmacokinetic-pharmacodynamic properties of oral dihydroru·temisinin were compared with oral artesunate (4 mg/kg) in a crossover study in Thai healthy volunteers (n=20) and in patients with acute, uncomplicated malaria (n=20) admitted to the Hospital of Tropical diseases, Bangkok. The drugs were given sequentially once daily (day 1 DHA, day 2 AS or vice versa). For patients, mefloquine (MQ) 25 mg/kg was administered as a split dose on the third day to complete the treatment.

The maximum effect (Cmax) associated with DHA (1,576 nM) is less than that of AS (4,042 nM) in normal volunteers (p < 0.001), but it is comparable to AS in patients (3,377 vs 5,400 nM, p 0.04). The time to reach maximum effect (tmax) for both drugs in normal volunteers and patients are 0.5 - 3 and 0.5 - 8 hr respectively. The elimination half-Jive's (t1/2,z) of the effect associated with both drugs are between 1 - 2.6 hr in volunteers. Although in patients, the half-live's of DHA are not different than in volunteers (p > 0.05), there are wide variation in the half-live's associated with AS in patients compared to volunteers (0.5 - 4.0 h). The areas under the effect-time curves corrected for molar dose (AUC/D) of DHA in both volunteers and patients (0.394 and 0.804 h.kg.L-1 , respectively) are less than AS (0.654 and 1.114 h.kg.L-1, respectively; p < 0.001). The relative bioavailability of the effect associated with DHA is 70% and 80% of AS in volunteers and patients, respectively.

The apparent volume of distribution (Vz/f) of the effect associated with DHA is 2 fold greater than AS (6.8 VS 2.7 L.kg-1 in normal volunteers, p = 0.001; and 2.6 VS 1.6 L.kg-1 in patients, p = 0.005). The clearance (Cl/f) of the DHA effect is faster than that of AS in normal volunteers (3.0 VS 1.7 L.kg-1.h-1 , p < 0.001) but it is not clinically different in patients (1.3 VS 1.0 L.kg-1.h-1 , p = 0.01). The volume of distribution and clearance associated with DHA are reduced by half in patients with malaria compared to volunteers (6.79 VS 2.57 L.kg-1 and 3.03 VS 1.33 L. kg-1.h-1 , p = 0.001 and < 0.001, respectively). Both parameters for AS are also reduced in patients but to a lesser extent than DHA (2.68 VS 1.59 L.kg·1 and 1.72 VS 1.01L. kg-1.h-1 , p=0.004 and= 0.006, respectively).

In summary, effect kinetic bioavailability of oral DHA is 80% of oral AS in patients. If the production cost of DHA is, in fact significantly less than AS, DHA can be regarded as comparable to or economically better than AS.