Study on Cross-resistance of Piperaquine and Lumefantrine resistant *Plasmodium berghei* and selection of Amodiaquine resistance in a mouse model

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ABSTRACT

Over the last two decades, malaria prevalence has increased and distribution expanded due to the spread of multi-drug resistant *Plasmodium falciparum*.

Following selection of stable piperaquine (PQ) and lumefantrine (LM)-resistant *P.berghei* ANKA lines through drug pressure, the current study sought to establish cross-resistance patterns between the two resistant lines with antimalarials; chloroquine (CQ), amodiaquine (AQ), dihydroartemisinin (DHA), atovaquone (ATQ), primaquine (PMQ) and LM or PQ. The activity of the drugs; against both sensitive and PQ and LM resistant lines (after 10 drug free passages) were assessed in the 4-day test (4-DT), and index of resistance, I90 determined. Analysis of crossresistance patterns showed a significant decrease in CQ (I90 of 1.62), ART (I90 of 5.36) and PMQ (I90 of 6.39) activity against LM-resistant line. However, AQ (I90 of 1.06), PQ (I90 of 0.91) and ATQ (I90 of 1.19) maintained their potency.

On therapeutic aspect, the findings of the study imply that if LM component of Coartem® selects for resistance, then the drug to use in clearing these LM-resistant parasites could be Artekin® that has PQ as its component. However, in the study cross-resistance exists between ART and LM, thus putting the artemisinin combination therapy in a precarious position. But the most ideal compounds to use in case of LM-resistance are ATQ and AQ. On the other hand, selection of PQ resistance was associated with a significant reduction in efficacy of LM (I90 of 97.25), PMQ (I90 of 12.22), CQ (I90 of 7.35), AQ (I90 of 3.62) and DHA (I90 of 2.96).

Selection of PQ-resistance is associated with resistance of LM, PMQ, CQ, AQ and DHA. However, ATQ retained its potency against PQ resistant line, although with slight insignificant differences from that of the parent strain. Thus, ATQ will be the drug of choice to use in places where PQ-resistance has emerged. Overall, ATQ seems to have retained considerable sensitivity

in the face of PQ and LM-resistance development in *P. berghei*. Consequently, ATQ should be considered favorably in future as a partner drug to artemisinin in ACT therapy. When the findings of the study were analyzed and related to previous work involving *P. falciparum* malaria, it was deduced that the selected PQ and LM-resistant *P. berghei* strains are significantly related to that of *P. falciparum*. The findings therefore support the use of a mouse model as a surrogate in studying drug resistance for PQ and LM.

The results of this study strongly suggest that the mechanism of resistance of LM and PQ

in *P. berghei* be clarified in a different study.

Besides cross-resistance studies, the current study sought to select using serial technique (ST) method a *P. berghei* ANKA strain that is 'resistant' to AQ. The level of resistance was assessed at different intervals by the measurement of I99 in the standard 4-DT. The stability of AQ resistant line was evaluated by measuring drug responses (ED99) using a 4-DT, after making 10 drug free passages. The study concluded that it is difficult to select a stable AQ resistant phenotype. Subsequently, a different approach other than ST be adopted in the selection of AQ resistance.