Thesis title : COMPARATIVE INHIBITORY EFFECTS OF MEFLOQUINE AND PRIMAQUINE ON HEPATIC DRUG-METABOLIZING ENZYMES

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ABSTRACT

The effect of mefloquine (MQ) on hepatic drug-metabolizing enzymes in the rat has been compared with that of primaquine (PQ) both in vitro and in vivo. For in vitro studies using type I compounds (aminopyrine and hexobarbital), it was found that MQ inhibited only aminopyrine N-demethylase whereas PQ inhibited both aminopyrine N-demethylase and hexobarbital oxidase. At the concentration of 10^{-4} M these two antimalarials produced comparable per cent inhibition (approximately 54%) on aminopyrine N-demethylase, while at the lower concentration PQ produced greater inhibition than MQ. As for type

II compounds (aniline and p-chloro-N-methylaniline), MQ exerted a very weak inhibitory effect on aniline hydroxylase (23% at 10^{-4}M) but had no effect on p-chloro-N-methylaniline N-demethylase. On the contrary, PQ was found to be quite a potent inhibitor of aniline hydroxylase but to be a very weak inhibitor of p-chloro-N-methylanline N-demethylase (11% at 10^{-4} M). For a reverse type I compound, p-nitroanisole, both MQ and PQ could inhibit the enzyme p-nitroanisole-O-demethylase, though MQ was a very weak inhibitor. Kinetic studies showed that aminopyrine N-demethylase was inhibited noncompetitively by MQ whereas the inhibition by PQ was competitive. PQ was also found to be a noncompetitive inhibitor of hexobarbital oxidase, while producing a noncompetitive and competitive inhibition on aniline hydroxylase and p-chloro-N-methylaniline N-demethylase, respectively. The kinetic nature of inhibition by both MQ and PQ on the metabolism of the reverse type I compound was noncompetitive.

The results from studies <u>in vivo</u> were consistent with the <u>in vitro</u> findings. PQ (50 mg/kg, IP) was found to prolong zoxazolamine paralysis time while MQ (50mg/kg, PO) had no effect. These findings thus demonstrate that MQ is a much weaker inhibitor of hepatic drug-matabolizing enzymes than PQ.