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ORIGINAL PAPER

The use of a prodrug approach to minimize potential CNS exposure of next generation quinoline methanols while maintaining efficacy in in vivo animal models

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Abstract The use of mefloquine (MQ) for antimalarial treatment and prophylaxis has diminished largely in response to concerns about its neurologic side effects. An analog campaign designed to maintain the efficacy of MQ while minimizing blood–brain barrier (BBB) penetration has resulted in the synthesis of a prodrug with comparable-to-superior in vivo efficacy versus mefloquine in a *P. berghei* mouse model while exhibiting a sixfold reduction in CNS drug levels. The prodrug, WR319670, performed poorly compared to MQ in in vitro efficacy assays, but had promising in vitro permeability in an MDCK–MDR1 cell line BBB permeability screen. Its metabolite, WR308245, exhibited high predicted BBB penetration with excellent in vitro efficacy. Both WR319670 and WR308245 cured 5/5 animals in separate in vivo efficacy studies. The in vivo efficacy of WR319670 was thought to be due to the formation of a more active metabolite, specifically WR308245. This was supported by pharmacokinetics studies in non-infected mice, which showed that both IV and oral administration of WR319670 produced essentially identical levels of WR319670 and WR308245 in both plasma and brain samples at all time points. In these studies, the levels of WR308245 in the brain were 1/4 and 1/6 that of MQ in similar IV and oral studies, respectively. These data show that the use of WR319670 as an antimalarial prodrug was able to maintain efficacy in in vivo efficacy screens, while significantly lowering overall penetration of drug and metabolites across the BBB.

Keywords Malaria · Mefloquine · Quinoline methanol · Blood–brain barrier · Central nervous system · Prodrug

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1 Introduction

According to current Centers for Disease Control and Prevention guidelines (Arguin 2012), mefloquine (MQ) (Fig. 1a) is arguably the most widely applicable drug for malaria chemoprophylaxis for non-immune individuals traveling to endemic countries. Like chloroquine (CQ), MQ can be administered on a weekly basis, a characteristic that enhances the likelihood of compliance and is more forgiving in cases of late or missed dosages. Further, both drugs are deemed safe for children of all ages/sizes and for

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