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Drug interactivity studies to define synergistic anti-malarial combinatorial regimes for Emetine dihydrochloride

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The emergence and spread of artemisinin resistance to Plasmodium falciparum in Southeast Asia poses a serious threat to ongoing malaria control efforts. Unless new approaches are deployed rapidly, the health and economic burden related to the disease in tropical countries is certain to worsen. The development of treatments through drug repositioning may offer novel candidates permitting new combinatorial regimes with existing anti-malarials. The approach could present a much needed viable, accelerated route to expand the dwindling antimalarial therapeutic repertoire. Drug repositioning screens previously carried out in our laboratory reported the potent antimalarial efficacy (IC50 47nM for P. falciparum K1 strain) of the anti-amoebic drug Emetine dihydrochloride hydrate. We present here the preliminary data from a study designed to define the combinatorial therapeutic potential of emetine with a panel of antimalarial drugs, in a bid to minimise non-target effects previously experienced with the use of the drug in amoebiasis. The rational discovery of novel synergistic drug combinations can be accelerated by predictions of combination effects through experimental studies. All combinations were analysed using the optimized CalcuSyn fixed-ratio method validated using the atovoquone-proguanil combination. Following a screen of current antimalarial compounds, our preliminary data identified AN16 as the combinatorial partner drug displaying maximum synergistic interactivity with emetine dihydrochloride. The isobologram plot and the combination index (CI) generated by the CalcuSyn software demonstrated that the interaction between emetine and AN16 is synergistic at IC50, 1C75 and IC90 levels. The MTT cytotoxicity results indicated that the emetine- AN16 combination has a better selectivity index in comparison to emetine alone. The results strongly support further in vivo investigation of the utility of emetine-AN16 combination as an alternative antimalarial treatment for drug resistance malaria.

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