Quinoline Drugs Modulate Heme Toxicity

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Plasmodium parasites digest vertebrate blood and release heme molecules inside their acidic (pH 4.8) food vacuole. "Free heme" exert many toxic effects, causing oxidative stress-dependent and independent damage. In this parasite, the main heme detoxification mechanism consist on its crystallization into a pigment named hemozoin (Hz). Quinoline drugs interact with "free heme", forming a complex that not only avoids its crystallization but also increases heme association with membranes, eventually leading to parasite death. Previous work indicated that the antimalarial effect of chloroquine (CQ) is independent of oxidative stress conditions. Also, recent evidence have shown that quinine (QN) and CQ interact differently with heme. Here, we investigated the effects of quinoline binding on heme reactivity at a physiologically relevant pH (4.8) and a non-physiological pH (7.4). Both quinoline drugs increased the hemolytic effects of heme, particularly at lower concentrations, in a mechanism independent of oxidative stress at pH 7.4. Lipid peroxidation, assessed by heme-induced oxygen consumption, revealed that only QN, but not CQ, strongly inhibited lipid peroxidation at pH 4.8 using linolenic acid as substrate. At pH 7.4, both QN and CQ strongly inhibited heme-induced oxygen consumption. Similar data were found using oleic acid as substrate. These results indicate that heme toxic effects are modulated by different associations with antimalarial quinolines. Importantly, the current knowledge over the antimalarial effects of quinolines must be re-evaluated since our data strongly indicate that a quinoline methanol forms a complex with heme that reduces its pro-oxidant effects.

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