Exogenous iron increases fasciocidal activity and hepatocellular toxicity of the synthetic endoperoxides OZ78 and MT04

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The synthetic peroxides OZ78 and MT04 recently emerged as fasciocidal drug candidates. However, the effect of iron on fasciocidal activity and hepatocellular toxicity of these compounds is unknown. We investigated the in vitro fasciocidal activity and hepatocellular toxicity of OZ78 and MT04 in absence and presence of Fe(II)chloride and hemin, and conducted a toxicological study in mice. Studies were performed in comparison with the antimalarial artesunate (AS), a semisynthetic peroxide. Fasciocidal effects of OZ78 and MT04 were confirmed and enhanced by Fe; 2+; or hemin. In HepG2 cells, AS reduced cellular ATP and impaired membrane integrity concentration-dependently. In comparison, OZ78 or MT04 were not toxic at 100 ţM and reduced the cellular ATP by 13% and 19%, respectively, but were not membrane-toxic at 500 ţM. The addition of Fe; 2+; or hemin increased the toxicity of OZ78 and MT04 significantly. AS inhibited complex I, II, and IV of the mitochondrial electron transport chain, and MT04 impaired complex I and II, whereas OZ78 was not toxic. All three compounds increased cellular reactive oxygen species (ROS) concentration-dependently, with a further increase by Fe; 2+; or hemin. Mice treated orally with up to 800 mg OZ78, or MT04 showed no relevant hepatotoxicity. In conclusion, we confirmed fasciocidal activity of OZ78 and MT04, which was increased by Fe; 2+; or hemin. OZ78 and MT04 were toxic to HepG2 cells, which was explained by mitochondrial damage associated with ROS generation in the presence of iron. No relevant hepatotoxicity was observed in mice in vivo, possibly due to limited exposure and/or high antioxidative hepatic capacity.
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