

Safety of inhaled ivermectin as a repurposed direct drug for treatment of COVID-19: A preclinical tolerance study

Uw/cp"Ocpuqwt".Tg jcd"P"Ujcooc"4."Mcy mcd"C"Jogf"5."Pktoggp"C"
Ucdt{"6."Ico cn"Guocv"7."C//c"C"Ocj oqwf"8."Cot"Oci gf"9

Abstract

Replication of SARS-CoV-2 in cell cultures has been shown to be inhibited by ivermectin. However, ivermectin's low aqueous solubility and bioavailability hinders its application in COVID-19 treatment. Also, it has been suggested that best outcomes for this medication can be achieved via direct administration to the lung. Objectives: This study aimed at evaluating the safety of a novel ivermectin inhalable formulation in rats as a pre-clinical step. Methods: Hydroxy propyl- β -cyclodextrin (HP- β -CD) was used to formulate readily soluble ivermectin lyophilized powder. Adult male rats were used to test lung toxicity for ivermectin-HP- β -CD formulations in doses of 0.05, 0.1, 0.2, 0.4 and 0.8 mg/kg for 3 successive days. Results: The X-ray diffraction for lyophilized ivermectin-HP- β -CD revealed its amorphous structure that increased drug aqueous solubility 127-fold and was rapidly dissolved within 5 s in saline. Pulmonary administration of ivermectin-HP- β -CD in doses of 0.2, 0.4 and 0.8 mg/kg showed dose-dependent increase in levels of TNF- α , IL-6, IL-13 and ICAM-1 as well as gene expression of MCP-1, protein expression of PIII-NP and serum levels of SP-D paralleled by reduction in IL-10. Moreover, lungs treated with ivermectin (0.2 mg/kg) revealed mild histopathological alterations, while severe pulmonary damage was seen in rats treated with ivermectin at doses of 0.4 and 0.8 mg/kg. However, ivermectin-HP- β -CD formulation administered in doses of 0.05 and 0.1 mg/kg revealed safety profiles. Conclusion: The safety of inhaled ivermectin-HP- β -CD formulation is dose-dependent. Nevertheless, use of low doses (0.05 and 0.1 mg/kg) could be considered as a possible therapeutic regimen in COVID-19 cases.

International Immunopharmacology 2021, July