

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

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## Abstract

**Introduction:** SARS-CoV-2 replication 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- $\beta$ -cyclodextrin (HP- $\beta$ -CD) was used to formulate readily soluble ivermectin lyophilized powder. Adult male rats were used to test lung toxicity for ivermectin-HP- $\beta$ -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- $\beta$ -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- $\beta$ -CD in doses of 0.2, 0.4 and 0.8 mg/kg showed dose-dependent increase in levels of TNF- $\alpha$ , 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- $\beta$ -CD formulation administered in doses of 0.05 and 0.1 mg/kg revealed safety profiles. **Conclusion:** The safety of inhaled ivermectin-HP- $\beta$ -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.

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