Pharmacokinetic thoughts on the repurposing of oral ivermectin for treatment of COVID-19

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Abstract

None

A recent commentary published in BJCP used lopinavir/ritonavir as an example to highlight the importance of the clinical pharmacology principles in the repurposing of old drugs for therapeutic use against Coronavirus disease 19 (COVID-19).[1] Here, we provide another example to support this point.

A recent study found that ivermectin, an FDA-approved anti-parasitic drug, has inhibitory effects on the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] Ivermectin has broad anti-viral activity through inhibition of viral proteins including importin α/β1 heterodimer and integrase protein.[3] In the *in vitro* study reported by Caly and colleagues, the addition of ivermectin at a concentration of 5 micromolar (μM) (twice the reported IC50) to Vero-hSLAM cells 2 hours post infection of with SARS-CoV-2 resulted in a reduction in the viral RNA load by 99.98% at 48 hours.[2]

Large trials of mass drug administration of ivermectin in adults and children have shown that ivermectin is well tolerated.[4] Even at doses that are 10 times greater than the highest FDA-approved dose of 200 μg/kg, central nervous system toxicity has not been reported.[5] However, following the oral administration of supra-therapeutic doses of ivermectin (i.e. 120 mg) the maximum plasma concentration achieved was 0.28 ± 0.18 (standard deviation) μM, a value 18 times lower than the reported 5 μM ivermectin concentration used by Caly *et al* in their SARS-CoV-2 experiment.[5] To date, the clinical effects of ivermectin at a concentration of 5 μM range are unknown, but likely to be toxic. Furthermore, ivermectin is only commercially available as a 3 mg oral tablet.[6] These factors hinder our ability to immediately repurpose ivermectin in its current form for the treatment of COVID-19.

While the findings by Caly and colleagues provide some promise, viral suppression was not seen at concentrations observed with standard doses in humans. Further preclinical *in vivo* studies should evaluate the pharmacokinetics and pharmacodynamics to determine the kill pattern of ivermectin. A potential alternate solution may be to develop an inhaled formulation of ivermectin to efficiently deliver a high local concentration in the lung, whilst minimising systemic toxicity. As therapeutic agents to tackle the COVID-19 pandemic are urgently sought, careful consideration of the pharmacokinetics of these drugs should be considered to guide *in vitro* testing.

Conflict of interest

None

References:

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