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LETTER TO THE EDITOR

Pharmacokinetic considerations on the repurposing of ivermectin for treatment of COVID-19

Hundreds of researchers are working to develop a vaccine and are evaluating drugs to mitigate the adverse health and economic consequences of COVID-19 (Coronavirus disease 19) worldwide. If novel compounds are found, geopolitical and economic variables will determine their introduction to communities. Therefore, finding low-cost and widely accessible drugs for prevention or treatment of COVID-19 would be ideal.

A recent study found that ivermectin, an FDA-approved antiparasitic drug, has inhibitory effects on replication of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Ivermectin has broad anti-viral activity through inhibition of viral proteins including importin α/β1 heterodimer and integrase protein.[2] Caly and colleagues reported that the addition of ivermectin at a concentration of 5μM (twice the reported IC_{50}) to Vero-hSLAM cells, 2 h post infection with SARS-CoV-2, resulted in a reduction in the viral RNA load by 99.98% at 48 h.[1] The authors suggested that this drug could reduce the viral load in infected patients, with potential effect on disease progression and spread.

While the findings by Caly and colleagues provide some promise, several pharmacokinetic factors limit the immediate translation of their findings, and there is no evidence that the 5μM concentration of ivermectin used by Caly and colleagues in their in vitro SARS-CoV-2 experiment, can be achieved in vivo. First, the pharmacokinetics of ivermectin in humans is well described,[3–5] and even with the highest reported dose of approximately 1700 μg/kg (i.e., 8.5 times the FDA-approved dose of 200 μg/kg), the maximum plasma concentration was only 0.28μM.[5] Second, 93% of ivermectin is bound to plasma proteins that limit its cellular uptake by endothelial cells.[6] Considering both the total plasma concentration and protein binding, the free plasma concentration of ivermectin would be 250 times lower than the concentration required to reduce viral replication of SARS-CoV-2 in vitro (Figure 1). Third, whilst there is no data on the tissue penetration of ivermectin in human lungs, the total concentration of ivermectin in calves injected with 200 μg/kg reached only 100 ng/g (approx. 0.1μM) in lung tissue, which suggests that its accumulation would not be sufficient to achieve the antiviral effect with conventional doses.[7] Although high doses of ivermectin in adults or children are well tolerated,[5,8] the clinical effects of ivermectin at a concentration of 5μM range are unknown and may be associated with toxicity. Consequently, ivermectin has in vitro activity against SARS-CoV-2, but this effect is unlikely to be observed in vivo using current dosing.

Amidst fear of the pandemic, the public and some physicians are now using ivermectin off-label for prophylaxis or as adjuvant therapy for COVID-19. Because ivermectin is only commercially available as a 3 or 6 mg tablets or a 6 mg/ml oral suspension, in order to administer a high dose, some people may experiment with more concentrated veterinary formulations. These actions are not based on clinical trials and have motivated cautionary statements from institutions such as the FDA against the use of pharmaceutical formulations of ivermectin intended for animals as therapeutics in humans.[9]

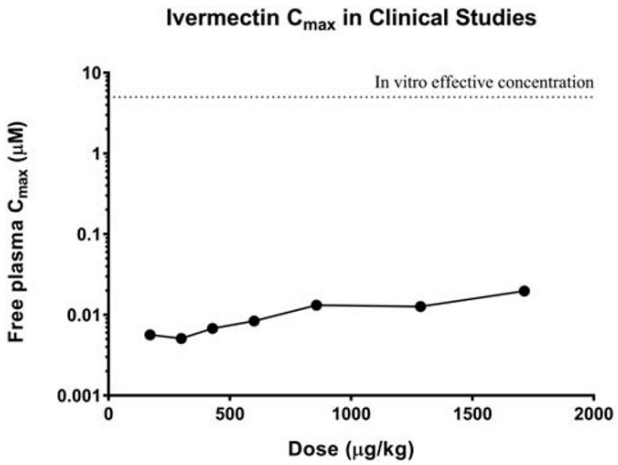

FIGURE 1 Expected free plasma concentrations of ivermectin based on 93% binding to plasma proteins and previously published total plasma concentrations.[3–5] When necessary, an estimated body weight of 70 kg was used for calculations. Note that none of the doses reached the 5μM concentration required for the antiviral effect of ivermectin (dotted line)

Potential avenues for further investigation into repurposing ivermectin for SARS-CoV-2 may be to (i) develop an inhaled formulation to efficiently deliver a high local concentration in the lung, whilst minimizing systemic exposure and (ii) evaluate synergistic effects of ivermectin with other compounds that also inhibit SARS-CoV-2 replication. With 18 registered clinical trials (clinicaltrials.gov) evaluating ivermectin for the treatment of COVID-19, this letter highlights the critical need to consider pharmacological principles to guide in vitro and clinical testing when repurposing old drugs for therapeutic use for the SARS-CoV-2 pandemic.[10]

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

R.P.-S., S.B.D, A.C.S., S.X.J.-R., A.G., and X.Z. conceived the idea and designed the study. R.P.-S., S.X.J.-R., X.Z., and A.G. collected data and drafted the manuscript, and R.P.-S. and X.Z. worked on the figures. R.P.-S., S.B.D., A.C.S., S.X.J.-R., A.G., and X.Z. reviewed and approved the manuscript.

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REFERENCES

1. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res*. 2020;178:104787.
2. Wagstaff KM, Rawlinson SM, Hearps AC, Jans DA. An AlphaScreen(R)-based assay for high-throughput screening for specific inhibitors of nuclear import. *J Biomol Screen*. 2011;16(2):192-200.
3. Smit MR, Ochomo EO, Waterhouse D, et al. Pharmacokinetics-pharmacodynamics of high-dose Ivermectin with dihydroartemisinin-piperaquine on mosquitocidal activity and QT-prolongation (IVERMAL). *Clin Pharmacol Ther*. 2019;105(2):388-401.
4. Duthaler U, Suenderhauf C, Karlsson MO, et al. Population pharmacokinetics of oral ivermectin in venous plasma and dried blood spots in healthy volunteers. *Br J Clin Pharmacol*. 2019;85(3):626-633.
5. Guzzo CA, Furtek CI, Porras AG, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol*. 2002;42(10):1122-1133.
6. Audus KL, Knaub SR, Guillot FL, Schaeffer JM. The effect of protein binding on ivermectin uptake by bovine brain microvessel endothelial cells. *Vet Res Commun*. 1992;16(5):365-377.
7. Lifschitz A, Virkel G, Sallovitz J, et al. Comparative distribution of ivermectin and doramectin to parasite location tissues in cattle. *Vet Parasitol*. 2000;87(4):327-338.
8. Weil GJ, Bogus J, Christian M, et al. The safety of double- and triple-drug community mass drug administration for lymphatic filariasis: a multicenter, open-label, cluster-randomized study. *PLoS Med*. 2019;16(6):e1002839.
9. Solomon S. FDA letter to stakeholders: do not use Ivermectin intended for animals as treatment for COVID-19 in humans. 2020. https://www.fda.gov/animal-veterinary/product-safety-information/fda-letter-stakeholders-do-not-use-ivermectin-intended-animals-treatment-covid-19-humans. Accessed April 15, 2020.
10. Smith PF, Dodds M, Bentley D, Yeo K, Rayner C. Dosing will be a key success factor in repurposing antivirals for COVID-19. *Br J Clin Pharmacol*. 2020. https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.14314