

Title Page

Title: The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19

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Abstract

Caly, Druce (1) reported that ivermectin inhibited SARS-CoV-2 *in vitro* for up to 48 h using ivermectin at 5 μ M. The concentration resulting in 50% inhibition (IC₅₀, 2 μ M) was >35x higher than the maximum plasma concentration (C_{max}) after oral administration of the approved dose of ivermectin when given fasted. Simulations were conducted using an available population pharmacokinetic model to predict total (bound and unbound) and

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unbound plasma concentration-time profiles after a single and repeat fasted administration of the approved dose of ivermectin (200 $\mu\text{g}/\text{kg}$), 60 mg, and 120 mg. Plasma total C_{max} was determined and then multiplied by the lung:plasma ratio reported in cattle to predict the lung C_{max} after administration of each single dose. Plasma ivermectin concentrations of total (bound and unbound) and unbound concentrations do not reach the IC_{50} , even for a dose level 10x higher than the approved dose. Even with the high lung:plasma ratio, ivermectin is unlikely to reach the IC_{50} in lungs after single oral administration of the approved dose (predicted lung: 0.0873 μM) or at doses 10x higher than the approved dose administered orally (predicted lung: 0.820 μM). In summary, the likelihood of a successful clinical trial using the approved dose of ivermectin is low. Combination therapy should be evaluated *in vitro*. Re-purposing drugs for use in COVID-19 treatment is an ideal strategy but is only feasible when product safety has been established and experiments of re-purposed drugs are conducted at clinically relevant concentrations.

Introduction

Recently, an article by Caly, Druce (1) reported that ivermectin inhibited SARS-CoV-2 *in vitro* causing a ~5000-fold reduction in viral RNA at 48 h with ivermectin at 5 μM . The concentration resulting in 50% inhibition (IC_{50}) of 2 μM (1750 ng/mL) is >35x higher than the maximum plasma concentration (C_{max}) of 0.05 μM (46.6 ng/mL (2)) after oral administration of the approved dose (~200 $\mu\text{g}/\text{kg}$) and ivermectin showed little to no activity 1 μM *in vitro*. Since ivermectin is highly bound to serum albumin (93%, (3)), the IC_{50} is orders of magnitude higher than the unbound plasma C_{max} after approved doses of ivermectin (0.0035 μM ; 3.26 ng/mL).

In order to understand how *in vitro* SARS-CoV-2 inhibition by ivermectin translates to humans, one must first evaluate these concentrations compared to predicted lung concentrations in humans after oral administration of ivermectin. Theoretically, only unbound drug in the plasma could access the lung and other tissues through passive diffusion. Ivermectin reaching the lung after oral dosing is also likely related to lipophilicity (which is high), the low ionization at physiologic pH, the binding of ivermectin to proteins in the lung (which is unknown), and any transporter(s) that may help maintain tissue distribution (which is unknown). While ivermectin concentrations in lung tissue cannot be measured in humans, ivermectin exposure in homogenates obtained from the left diaphragmatic lung was reported to be 2.7x higher than total plasma exposure in cattle after a single dose (4). Even with these higher concentrations in lung, ivermectin is unlikely to reach the IC₅₀ after oral administration of the approved dose in humans.

Unlike the narrow therapeutic index for hydroxychloroquine and chloroquine, ivermectin has a wider safety margin (2). The safety of higher doses of ivermectin has been evaluated in a Phase 3 study, where 200-400 µg/kg doses were studied in patients with Dengue fever (5, 6). Even higher doses (up to 10x higher than approved doses) were studied in a small Phase 1 trial (7). This trial showed that ivermectin administered orally in the fasted state was well tolerated both after a single 120 mg dose (10x higher than approved dose) and after 60 mg three times weekly (every 72 hours). The most common adverse events were headache, nausea, dizziness, and rash. The reported incidence and type of adverse events were relatively similar between ivermectin (24%) and placebo (35%) and did not increase with dose. All dosing regimens had a mydriatic effect (the primary safety endpoint based on results from toxicology studies) similar to placebo. It is important to note that while this

study evaluated common adverse events, the presence and incidence of rare adverse events at these high doses are unknown, given the small number of subjects studied.

The overall objective of this analysis was to evaluate what doses in humans would be predicted to result in lung concentrations reaching the IC₅₀ in the lungs to help in designing a successful clinical trial with ivermectin in the treatment of COVID-19.

Methods:

A population pharmacokinetic model for ivermectin reported by Duthaler, Suenderhauf (8) was used in the simulations. This model was a two-compartment model with a transit absorption model, first-order elimination, and weight as a covariate on central volume of distribution and clearance. This model was developed from healthy subjects with a median age of 23 (range: 20 to 36) years and median weight of 64.7 (range: 57.3-94.2) kg receiving a single ivermectin dose of 12 mg in the fed state.

Simulations (n=500) were performed using NONMEM version 7.4 (ICON Development Solutions, Ellicott City, MD). Total (bound and unbound) plasma concentration-time profiles were simulated to predict exposure for the approved dose of ivermectin (200 µg/kg, in 3 mg increments) and 120 mg (studied by Guzzo, Furtek (7) as single doses). Since ivermectin concentrations remained steady in cattle lungs for 8 days and then declined over an additional 30 days after a single subcutaneous dose (4), additional simulations were conducted to predict plasma concentrations with weekly dosing. In addition, 60 mg administered three times weekly was simulated (every 72 hours), given this dose was studied in healthy subjects by Guzzo, Furtek (7).

A range of body weights in adults was sampled from the Center for Disease Control weight chart for 20 year old adults, with male:female ratio being 1:1 (9). The median (3rd and 97th percentiles) weights were 70.6 (54.0-101) kg in males and 58.2 (45.0-89.0) kg in females, which represent most adults but does not include morbidly obese patients.

Predicted concentrations required correction for the fact that the population pharmacokinetic model was built based on subjects who received ivermectin with a high-fat breakfast, yet ivermectin should be taken on an empty stomach (2). Bioavailability of ivermectin is increased by 2.57-fold increase in fed state with no change in T_{max} and parallel concentration-time curves (7) (suggesting a change in extent of absorption, but not rate of absorption). Therefore, all plasma concentration-time data were divided by the geometric least squares mean ratio of AUC_{inf} fed:fasted (2.57) to predict concentrations when ivermectin is administered in the fasted state.

Unbound plasma concentration-time data were predicted by multiplying the total concentration by the unbound fraction in plasma (0.068).

The C_{max} values for total plasma concentration were determined and multiplied by the lung homogenate:plasma ratio (2.67:1) in cattle reported by Lifschitz, Virkel (4) at each single dose to derive the C_{max} values for total lung concentrations. The lung:plasma ratio after repeat dosing could not be determined without further modeling of the data from cattle.

Some accumulation is expected in lung (but not plasma) with weekly or 3x weekly administration, but needs further investigation with more experimental data. A ball-park accumulation ratio (AR) in lung was calculated using Equation 1:

Equation 1
$$AR = \frac{1}{1 - \exp^{-ke \cdot \tau}}$$

Where k_e is the estimated elimination rate constant from the cattle lung concentration-time profile presented by Lifschitz, Virkel (4) and τ is the dosing interval.

Results

Plasma ivermectin concentrations of total (bound and unbound) and unbound concentrations do not reach the IC_{50} reported by Caly, Druce (1), even for dose level 10x higher than the approved dose, or after repeat dosing (Figure 1). Plasma exposures did not increase substantially after repeat dosing, with very limited ivermectin accumulation in plasma after 3 times weekly or weekly dosing.

Even with the high lung homogenate:plasma ratio, ivermectin is unlikely to reach the IC_{50} of 2 μM in the lung after single oral administration of the approved dose (predicted lung concentration: 0.0873 μM) or at doses 10x higher than the approved dose administered orally (predicted lung concentration: 0.820 μM) (Table 1). Currently there is no lung tissue disposition data available after repeated dosing, but the ballpark accumulation ratio in lungs can be used to predict lung concentrations relative to the IC_{50} after repeat dosing. If the approved dose was administered weekly, the ball-park accumulation ratio in lung tissue is 1.3, which would result in lung concentrations that are $1/20^{\text{th}}$ of the IC_{50} . If the approved dose was administered three times weekly, the ball-park accumulation ratio in lung tissue is 2.2, which would result in lung concentrations that are $1/10^{\text{th}}$ of the IC_{50} . If the approved dose was administered daily, the ball-park accumulation ratio in lung tissue is 5.35, which would result in lung concentrations that are $1/4^{\text{th}}$ of the IC_{50} . Using the ballpark accumulation ratio for higher doses, predicted lung concentrations would be $\sim 1/5^{\text{th}}$ the IC_{50} after 60 mg three times weekly or after 120 mg once weekly.

Discussion

The *in vitro* studies showing that ivermectin inhibited SARS-CoV-2 (1) were conducted at concentrations that were substantially higher than predicted plasma and lung concentrations in humans receiving the approved dose of ivermectin. Therefore, the likelihood of a successful clinical trial using the approved dose of ivermectin is low. If a clinical trial is conducted, a well-controlled dose-response study should be considered and the feasibility of ivermectin as an inhaled treatment should be evaluated.

A first step would be to conduct the *in vitro* study reported by Caly, Druce (1) evaluating whether other antivirals can potentiate ivermectin's inhibition of SARS-COV-2 to identify whether an ivermectin concentration of 0.1 μM (rather than 5 μM) with a concomitant antiviral can inhibit SARS-COV-2. Re-purposing drugs for use in the treatment of COVID-19 is an ideal strategy but is only feasible if the safety of the product use has been established at the dose levels that produce efficacy. Therefore, *in vitro* experiments of re-purposed drugs should be conducted at clinically relevant concentrations.

As soon as the *in vitro* findings were published, clinicians all over the world were using ivermectin off-label. Patel et al. reported this week through an observational registry-based study from 169 hospitals across the world that ivermectin 150 $\mu\text{g}/\text{kg}$ administered to 52 patients after institution of mechanical ventilation showed a potential decrease in hospital stay length and survival benefit compared to 1918 conventionally-treated patients (10). It is noted that these results did not account for co-morbidities that might account for these differences. Nevertheless, if ivermectin did contribute to these clinical findings, it would suggest that the *in vitro* findings by Caly, Druce (1) do not correlate with the very small amounts of the drug in lung tissue in humans, concentrations in lung homogenate do not

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correlate with concentrations at the site of action or those expected based on ivermectin's large volume of distribution, concentrations of drug do not need to reach the IC₅₀ for clinical benefit (i.e., the IC₅₀ is not relevant), distribution into or retention in the lung tissue of humans is greater than in cattle, or that accumulation in lung tissue is much greater (>20-fold) than expected after repeat dosing. Given that lung tissue:plasma concentration ratio in goats (3x at 2 and 7 days after oral administration) was similar to cattle and lung tissue:plasma concentration ratio in mice (1.4x 24 hours after oral administration) was slightly lower, excessive accumulation of ivermectin in human lungs is unlikely (11, 12).

If a clinical study is conducted with ivermectin, it would be important to conduct a well-controlled clinical dose-response study with ivermectin at a low dose (the approved dose, with lower likelihood of success) and at a higher dose relative to placebo in patients with COVID-19. The ideal higher dose of ivermectin has not been established. Ivermectin doses up to 120 mg have only been administered to a small number of subjects (7). After daily dosing of the ivermectin 200 µg/kg, lung concentrations are predicted to be around 1/4th of the IC₅₀. Daily dosing of ivermectin at the approved dose for longer periods (e.g., 14 days) have only been studied in small studies for serious infections where an unapproved subcutaneous formulation was used (13). Therefore, if higher doses are studied weekly, if the approved dose is studied daily, or a parenteral formulation is used, subjects will need to be monitored closely.

Ivermectin is extensively metabolized by CYP3A4 to numerous metabolites and is a substrate for P-glycoprotein. Less than 1% of the ivermectin dose is eliminated unchanged in the urine. Thus, any study would need to control for factors affecting variability in the exposure to ivermectin, including administering the dose in the fasted state and excluding P-

glycoprotein and CYP3A4 inhibitors (2), which could increase ivermectin exposure. The pharmacokinetics of ivermectin in elderly patients have not been reported. Theoretically, metabolism may decrease with age resulting in a higher exposure to ivermectin in elderly patients as well.

Lastly, a potential longer-term solution would be to consider whether inhaled treatment with ivermectin is feasible. Inhaled treatment would allow for higher concentrations at the site of action while limiting the systemic exposure but may require further study of the safety and tolerability in animals prior to human exposure. Only one nonclinical study has been published on inhaled ivermectin in Sprague Dawley rats, in which the no-observed-adverse-effect level (NOAEL) after 28 days of inhaled ivermectin was identified to be 380 mg/m³ (14), and no studies using the inhaled route of administration have been identified in humans. Of key importance is determining whether ivermectin has general properties that would allow inhalation, with no local tolerability issues. Experts must, therefore, evaluate whether ivermectin possesses the ideal properties for inhalation, and whether inhalation of ivermectin poses any theoretical risks that might limit this route of administration.

Overall, the results identified in the paper by Caly, Druce (1) create an opportunity for interdisciplinary collaboration in helping to understand the highest probability of success for ivermectin treatment, prior to exploration in clinical studies (or worse yet, off-label use by the general public) with a less-than-ideal dose.

Study Highlights

What is the current knowledge on the topic?

Caly, Druce (1) reported that ivermectin inhibited SARS-CoV-2 *in vitro* with an IC₅₀ which was >35x higher than the C_{max} after oral administration of the approved dose of ivermectin.

What question did this study address?

What ivermectin dose reaches the IC₅₀ in lungs after oral administration in humans.

What does this study add to our knowledge?

Ivermectin is unlikely to reach the IC₅₀ in lungs after oral administration of the approved dose or doses 10x higher than the approved doses as a single dose. The approved dose of ivermectin alone has a low probability of a success in the treatment of COVID-19.

How might this change clinical pharmacology or translational science?

Re-purposing drugs for use in COVID-19 treatment is an ideal strategy but is only feasible when product safety has been established and experiments of re-purposed drugs are conducted at clinically relevant concentrations.

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Figure Legend

Figure 1 Total (Bound and Unbound) and Unbound Plasma Ivermectin Concentrations Over Time Relative to the IC_{50} After Approved Doses of Ivermectin (200 $\mu\text{g}/\text{kg}$)

Administered Once Weekly (instead of as a Single Dose), and After Higher Doses Including 60 mg Every Three Days or 120 mg Once Weekly

Red dashed line= IC_{50} reported by Caly et al. (2020), 2 μM (1750 ng/mL). Blue shaded area and line=total plasma drug concentration and its 95% confidence interval (CI); red shaded area and line=free plasma drug concentration and its 95% CI.

Table 1 Predicted Maximum Total Plasma Concentrations and Lung Concentrations After Various Doses of Ivermectin Administered Fasted

Treatment		Predicted Total C _{max} (µM) Median [2.5 th , 97.5 th Percentiles]	
		Plasma	Lung ^b
Single Dose	200 µg/kg Single Dose (Labelled Dose)	0.0327 [0.0228, 0.0429]	0.0873 [0.0609, 0.115]
	120 mg Single Dose ^a	0.307 [0.204, 0.449]	0.820 [0.545, 1.20]
Repeated Dose (3 Weeks)	200 µg/kg Weekly	0.0334 [0.0230, 0.0439]	
	60 mg Every 72 hours ^a	0.169 [0.113, 0.248]	
	120 mg Weekly	0.313 [0.207, 0.462]	

^aEach Administered to 12 subjects (Guzzo et al., 2002)

^bCalculated based on reported lung:plasma ratio of 2.67 in cattle (Lifschitz et al., 2000).

CI = Confidence Interval

