




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

Virginia D. Schmith<sup>1,\*</sup> , Jie (Jessie) Zhou<sup>1</sup>  and Lauren R.L. Lohmer<sup>1</sup> 

Caly *et al.*<sup>1</sup> reported that ivermectin inhibited severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) *in vitro* for up to 48 hours using ivermectin at 5  $\mu\text{M}$ . The concentration resulting in 50% inhibition ( $\text{IC}_{50}$ ; 2  $\mu\text{M}$ ) was > 35 $\times$  higher than the maximum plasma concentration ( $C_{\text{max}}$ ) 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 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  $C_{\text{max}}$  was determined and then multiplied by the lung:plasma ratio reported in cattle to predict the lung  $C_{\text{max}}$  after administration of each single dose. Plasma ivermectin concentrations of total (bound and unbound) and unbound concentrations do not reach the  $\text{IC}_{50}$ , even for a dose level 10 $\times$  higher than the approved dose. Even with the high lung:plasma ratio, ivermectin is unlikely to reach the  $\text{IC}_{50}$  in the lungs after single oral administration of the approved dose (predicted lung: 0.0873  $\mu\text{M}$ ) or at doses 10 $\times$  higher than the approved dose administered orally (predicted lung: 0.820  $\mu\text{M}$ ). In summary, the likelihood of a successful clinical trial using the approved dose of ivermectin is low. Combination therapy should be evaluated *in vitro*. Repurposing drugs for use in coronavirus disease 2019 (COVID-19) treatment is an ideal strategy but is only feasible when product safety has been established and experiments of repurposed drugs are conducted at clinically relevant concentrations.

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Caly *et al.*<sup>1</sup> reported that ivermectin inhibited severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) *in vitro* with an 50% inhibition ( $\text{IC}_{50}$ ), which was > 35 $\times$  higher than the peak plasma concentration ( $C_{\text{max}}$ ) after oral administration of the approved dose of ivermectin.

### WHAT QUESTION DID THIS STUDY ADDRESS?

✓ What ivermectin dose reaches the  $\text{IC}_{50}$  in the lungs after oral administration in humans?

### WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✓ Ivermectin is unlikely to reach the  $\text{IC}_{50}$  in the lungs after oral administration of the approved dose or doses

10 $\times$  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 coronavirus disease 2019 (COVID-19).

### HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

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

Recently, an article by Caly *et al.*<sup>1</sup> reported that ivermectin inhibited severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) *in vitro* causing an  $\sim 5,000$ -fold reduction in viral RNA at 48 hours with ivermectin at 5  $\mu\text{M}$ . The concentration resulting in 50% inhibition ( $\text{IC}_{50}$ ) of 2  $\mu\text{M}$  (1,750 ng/mL) is > 35 $\times$  higher than the maximum plasma concentration ( $C_{\text{max}}$ ) of 0.05  $\mu\text{M}$  (46.6 ng/mL)<sup>2</sup> after oral administration of the approved dose ( $\sim 200$   $\mu\text{g}/\text{kg}$ ) and ivermectin showed little to no activity 1  $\mu\text{M}$  *in vitro*. Because ivermectin is highly bound to serum albumin (93%),<sup>3</sup> the  $\text{IC}_{50}$  is orders of magnitude higher than the unbound

plasma  $C_{\text{max}}$  after approved doses of ivermectin (0.0035  $\mu\text{M}$ ; 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 with predicted lung concentrations in humans after oral administration of ivermectin. Theoretically, only unbound drug in the plasma could access the lungs and other tissues through passive diffusion. Ivermectin reaching the lungs after oral dosing is also likely related to lipophilicity (which is high), the low ionization at physiologic pH, the binding of ivermectin to proteins

<sup>1</sup>Nuventra Pharma Sciences, Durham, North Carolina, USA. \*Correspondence: Virginia (Ginny) Schmith ([gschmith@nuventra.com](mailto:gschmith@nuventra.com))

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in the lungs (which is unknown), and any transporter(s) that may help maintain tissue distribution (which is unknown). Although ivermectin concentrations in lung tissue cannot be measured in humans, ivermectin exposure in homogenates obtained from the left diaphragmatic lung was reported to be 2.7× higher than total plasma exposure in cattle after a single dose.<sup>4</sup> Even with these higher concentrations in the lungs, ivermectin is unlikely to reach the IC<sub>50</sub> after oral administration of the approved dose in humans.

Unlike the narrow therapeutic index for hydroxychloroquine and chloroquine, ivermectin has a wider safety margin.<sup>2</sup> The safety of higher doses of ivermectin has been evaluated in a phase III study, where 200–400 µg/kg doses were studied in patients with Dengue fever.<sup>5,6</sup> Even higher doses (up to 10× higher than approved doses) were studied in a small phase I trial.<sup>7</sup> This trial showed that ivermectin administered orally in the fasted state was well-tolerated both after a single 120 mg dose (10× 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 end point based on results from toxicology studies) similar to placebo. It is important to note that although 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 IC<sub>50</sub> in the lungs to help in designing a successful clinical trial with ivermectin in the treatment of coronavirus disease 2019 (COVID-19).

## METHODS

A population pharmacokinetic model for ivermectin reported by Duthaler *et al.*<sup>8</sup> 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 the central volume of distribution and clearance. This model was developed from healthy subjects with a median age of 23 years (range 20–36 years) and median weight of 64.7 kg (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 *et al.*<sup>7</sup> as single doses). Because ivermectin concentrations remained steady in cattle lungs for 8 days and then declined over an additional 30 days after a single subcutaneous dose,<sup>4</sup> 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 *et al.*<sup>7</sup>

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.<sup>9</sup> The median (3rd and 97th percentiles) weights were 70.6 kg (54.0–101 kg) in men and 58.2 kg (45.0–89.0 kg) in women, 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.<sup>2</sup> Bioavailability of ivermectin is increased by 2.57-fold increase in the fed state with no change in time of maximum plasma concentration ( $T_{max}$ ) and parallel concentration-time curves<sup>7</sup> (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 the area under the curve to infinity ( $AUC_{inf}$ ) 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 *et al.*<sup>4</sup> 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 the lungs (but not plasma) with weekly or 3× weekly administration, but needs further investigation with more experimental data. A ball-park accumulation ratio (AR) in the lungs was calculated using Eq. 1:

$$AR = \frac{1}{1 - \exp^{-ke \cdot \tau}} \quad (1)$$

where  $ke$  is the estimated elimination rate constant from the cattle lung concentration-time profile presented by Lifschitz *et al.*<sup>4</sup> and  $\tau$  is the dosing interval.

## RESULTS

Plasma ivermectin concentrations of total (bound and unbound) and unbound concentrations do not reach the IC<sub>50</sub> reported by Caly *et al.*<sup>1</sup> even for dose level 10× 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 three times weekly or weekly dosing.

Even with the high lung homogenate:plasma ratio, ivermectin is unlikely to reach the IC<sub>50</sub> of 2 µM in the lungs after single oral administration of the approved dose (predicted lung concentration: 0.0873 µM) or at doses 10× 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 ball-park accumulation ratio in the lungs can be used to predict lung concentrations relative to the IC<sub>50</sub> 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 1/20th of the IC<sub>50</sub>. 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 1/10th of the IC<sub>50</sub>. 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 1/4th of the IC<sub>50</sub>. Using the ball-park accumulation ratio for higher doses, predicted lung concentrations would be ~ 1/5th the IC<sub>50</sub> after 60 mg three times weekly or after 120 mg once weekly.

## DISCUSSION

The *in vitro* studies showing that ivermectin inhibited SARS-CoV-2<sup>1</sup> 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 *et al.*<sup>1</sup> 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. Repurposing 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 repurposed drugs should be conducted at clinically relevant concentrations.

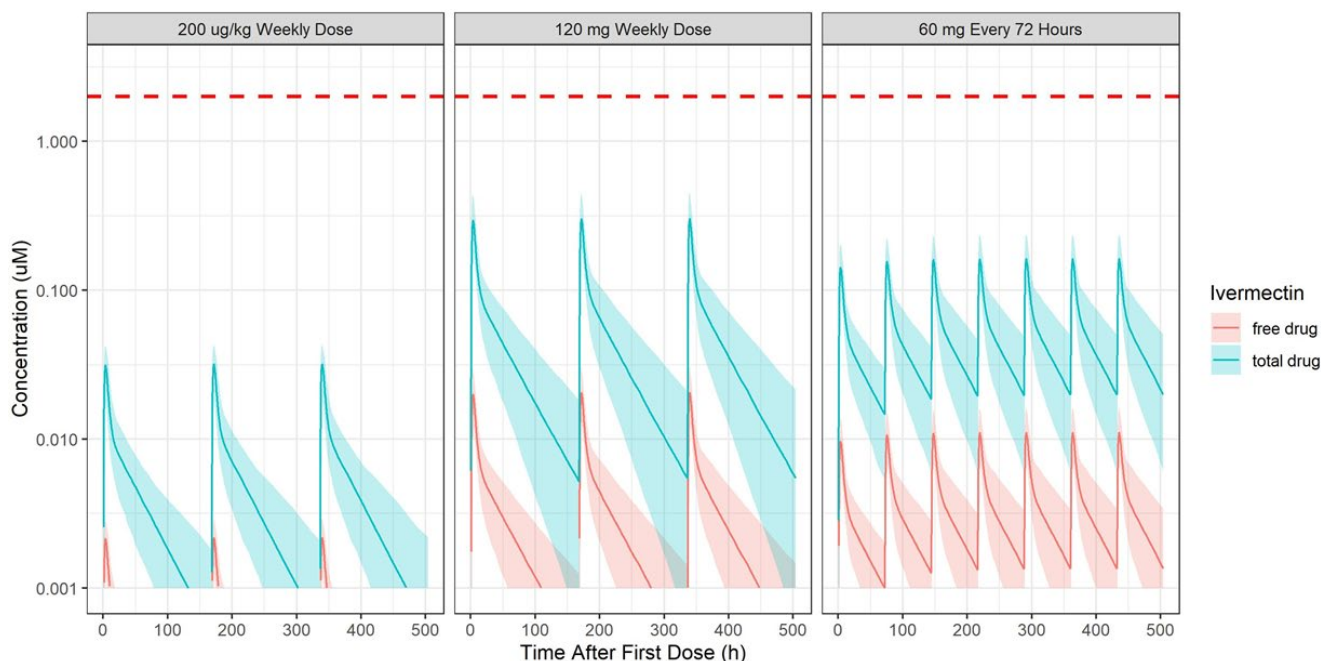
As soon as the *in vitro* findings were published, clinicians all over the world were using ivermectin off-label. Patel *et al.*<sup>10</sup> reported this week through an observational registry-based study from 169 hospitals across the world that ivermectin 150 μg/kg administered to 52 patients after institution of mechanical ventilation showed a potential decrease in hospital stay length and survival benefit compared with 1,918 conventionally treated patients.<sup>10</sup> It is noted that these results did not account for the comorbidities 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 *et al.*<sup>1</sup> do not correlate with the very small amounts of the drug in lung tissue in humans, concentrations in lung homogenate do not correlate with concentrations at the site of action or those

**Table 1 Predicted maximum total plasma concentrations and lung concentrations after various doses of ivermectin administered fasted**

Treatment	Predicted total C <sub>max</sub> (μM) Median [2.5th, 97.5th percentiles]	
	Plasma	Lung <sup>b</sup>
Single dose		
200 μg/kg single dose, labeled dose	0.0327 [0.0228, 0.0429]	0.0873 [0.0609, 0.115]
120 mg single dose <sup>a</sup>	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 <sup>a</sup>	0.169 [0.113, 0.248]	
120 mg weekly	0.313 [0.207, 0.462]	

C<sub>max</sub>, peak plasma concentration.  
<sup>a</sup>Each administered to 12 subjects (Guzzo *et al.*, 2002). <sup>b</sup>Calculated based on reported lung:plasma ratio of 2.67 in cattle (Lifschitz *et al.*, 2000).

expected based on ivermectin's large volume of distribution, concentrations of the drug do not need to reach the IC<sub>50</sub> for clinical benefit (i.e., the IC<sub>50</sub> 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)



**Figure 1** Total (bound and unbound) and unbound plasma ivermectin concentrations over time relative to the 50% inhibition (IC<sub>50</sub>) after approved doses of ivermectin (200 μg/kg) administered once weekly (instead of as a single dose), and after higher doses, including 60 mg every 3 days or 120 mg once weekly. Red dashed line = IC<sub>50</sub> 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.

than expected after repeat dosing. Given that lung tissue:plasma concentration ratio in goats ( $3\times$  at 2 and 7 days after oral administration) was similar to cattle and lung tissue:plasma concentration ratio in mice ( $1.4\times$  24 hours after oral administration) was slightly lower, excessive accumulation of ivermectin in human lungs is unlikely.<sup>11,12</sup>

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.<sup>7</sup> After daily dosing of the ivermectin 200  $\mu\text{g}/\text{kg}$ , lung concentrations are predicted to be around 1/4th of the  $\text{IC}_{50}$ . 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.<sup>13</sup> 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,<sup>2</sup> 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  $\text{mg}/\text{m}^3$ ,<sup>14</sup> 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 *et al.*<sup>1</sup> 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.

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#### CONFLICT OF INTEREST

V.S., L.L., and J.Z. are consultants and have worked with many companies but have not worked with companies who produce ivermectin orally (EDENBRIDGE PHARMS and MERCK). All authors declared no competing interests for this work.

#### AUTHOR CONTRIBUTIONS

G.S., J.Z., and L.L. wrote the manuscript. G.S. designed the research. J.Z. performed the research. J.Z. and L.L. analyzed the data.

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