COVID CONUNDRUM

# Antiviral pharmacokinetics vs dose and efficacy

## Because of the need for speed in a pandemic, drug development moves rapidly without due considerations

Repurposing of known drugs with antiviral activity against SARS-COV-2 has become a major focus for developing effective treatments during the pandemic. The standard development pathway for new drugs includes an examination of in vitro activity, pharmacodynamic activity in SARS-COV-2 infected animals, assessment of animal pharmacokinetics and toxicity, and Phase I, II & III trials in humans. Because of the need for speed in a pandemic, drug development moves rapidly from bench-in vitro to bedside-in vivo clinical trials without due consideration to the drug's dose-concentration-efficacy relationship.

To be clinically effective in COVID-19, a drug should reach therapeutic concentrations in the blood and the affected organ – lungs, in this case. For prophylaxis, the drug should be available in tissue concentrations sufficient to inhibit viral replication at multiple SARS-COV-2 infected sites - mucous membranes in the nasal cavity and throat, eyes, tears, and the upper respiratory tract and the lungs. In selecting an antiviral for clinical trials, the ratio of peak plasma concentration (Cmax) at an approved dose to EC90 effective concentration 90% and lung tissue Cmax/EC50 (half-maximal effective concentration) is important to consider. Arshad et al derived these ratios by pharmacokinetic modeling based on physiochemical and pharmacological parameters, and reported that the majority of the drugs — 42 out of 56 did not achieve plasma Cmax / EC90 > 1. These predicted ratios may not be achieved in COVID-19 patients because of altered pharmacokinetic processes - absorption, protein binding, distribution, metabolism & excretion - in patients suffering widespread multi-organ infection and receiving multiple therapies - antibiotics, steroids, oxygen & ventilator therapy. For example, the cellular uptake of chloroquine is markedly reduced in inflamed lungs characterized by acidic pH. Remdesivir concentrations in the lung are not adequate to kill the virus. The lack of correlation between lab data and clinically achievable plasma and lung concentrations could be a reason why drugs predicted to achieve high lung concentrations - hydroxychloroquine, chloroquine, ivermectin, azithromycin and lopinavir-ritonavir, have not shown consistent efficacy in clinical trials.

The gap between in-vitro antiviral concentration and effective in-vivo concentrations may suggest the need for using higher-than-approved doses for clinical practice. For ivermectin, achieving therapeutic plasma concentrations required for in vitro antiviral efficacy would require administration of doses much higher than the approved therapeutic range. In a pandemic setting, clinical trials involving higher-than-approved doses of antiviral agents may be justified if pharmacodynamic and pharmacodynamic data in SARS-COV-2 infected animal models are available. However, for most drugs, such data are not available. Hence, the use of high dose antivirals would be a safety risk for seriously ill COVID-19 patients with multi-organ involvement. Changing the route of administration to enhance availability of drug in plasma by intravenous administration or directly to lungs by nasal route would appear attractive. But this approach is not feasible during a pandemic as the new route too would require data on quality, stability, and human bioavailability, besides safety and dose optimization data for the new formulation, prior to conduct of clinical trials. This would be time consuming.

In summary, selecting an antiviral drug for repurposing requires a consideration of the complex interplay of in-vitro activity and in-vivo therapeutic concentrations in seriously ill patients!

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