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EDITORIAL COMMENTARY

Dose Optimization of Hydroxychloroquine for Coronavirus Infection 2019: Do Blood Concentrations Matter?

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Clinical trials of hydroxychloroquine (HCQ) for the treatment of coronavirus infection 2019 (COVID-19) are moving forward on the heels of conflicting, and sometimes controversial, observational studies out of China and France from the first months of the pandemic [1–3]. The most recent National Institutes of Health guidelines for COVID-19 state that current data are insufficient to recommend for or against the use of HCQ or its predecessor chloroquine (CQ) [4]. Given the extraordinary times, clinicians the world over may reach for either drug in desperation.

In this issue of *Clinical Infectious Diseases*, Martin-Blondel et al and Perinel et al present results of pharmacokinetic studies of HCQ with the intent of informing optimal dosing strategies for COVID-19 [5, 6]. Their intentions were sound. For most drugs, the concentration–response relationship is more informative than the dose–response relationship. Unfortunately, as has historically been the case with pharmacologic studies of HCQ, the current studies are bedeviled by the drug's extraordinary pharmacokinetics.

HCQ concentrations differed between the 2 studies by 4- to 8-fold for the same dosing regimen. Across all regimens, Martin-Blondel et al reported concentrations in the 40–240 ng/mL range compared with 1000–2000 ng/mL in the study by Perinel and colleagues. Martin-Blondel et al used plasma for their pharmacokinetic assays, whereas Perinel et al appear to have used whole blood, though this is not explicitly stated. Interpretation is further confounded by the different dosing regimens used in different patients.

In our 2018 article in this journal [7], we reported plasma concentrations of CQ, a structural analogue of HCQ with similar pharmacokinetics, measured by a validated liquid chromatography-tandem mass spectrometry assay, and concentrations were on the same order as those reported by Martin-Blondel et al [5]. In all 3 studies there was a broad range of concentrations, as is often reported for HCQ and related compounds. Different sampling matrices (plasma, whole blood) yield highly discrepant measurements of HCQ, and it is from this observation that we can begin to pull back the curtain on the idiosyncratic pharmacokinetics of HCQ that may consign the exercise at hand to uninterpretable outcomes.

Applying pharmacokinetic methods to optimize drug dosing is the preferred approach for most drugs. The alternative approach, predating the advent of clinical pharmacokinetics in the 1960s, is allometric and empirical. HCQ was developed in this earlier era, although it was still recognized for its extensive and unequal distribution with affinity for pigmented tissues and, important to note, lysosomes and other intracellular spaces [8].

HCQ is one of a small number of drugs for which the overwhelming driver of its pharmacokinetics is volume of distribution (V_d) rather than clearance. The typical V_d for HCQ is thousands to tens of thousands of liters for an average adult [9]. This imparts a long terminal elimination half-life, measured in weeks to months, despite relatively efficient renal and hepatic clearance. After a single 200-mg dose, HCQ remains detectable in urine for up to 3 months [10]. CQ, whose systemic pharmacokinetics are essentially indistinguishable from those of HCQ, remains detectable up to 1 year after the last dose of a typical malaria prophylaxis regimen [11].

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HCQ's enormous V_d is also the basis, in part, for the large interindividual variability in plasma and blood concentrations seen in the current studies and consistent with previous reports. Perinel et al speculate, justifiably, that the pharmacokinetics might further be altered by the pathophysiology of COVID-19. Then there is the potential role of enantiomeric differences in tissue distribution and drug effect, seen in other indications [12]. It is no wonder HCQ and CQ have vexed generations of clinical pharmacologists.

Because HCQ and CQ accumulate intracellularly, whole blood concentrations are several times higher than plasma concentrations and tend to be less variable from patient to patient [12]. Whole blood is therefore the preferred matrix for pharmacokinetic studies of HCQ [12]. Higher concentrations make detection and quantitation easier, and using whole blood avoids the variability introduced into the assay during plasma separation.

Yet blood concentrations are still a tiny sliver of a window into the presumed target tissues and cells for COVID-19 treatment and prevention. These would ostensibly be the type II pneumocytes of the alveoli and other virally infected cells throughout the body, if one believes that HCQ has direct antiviral activity. End organ tissue concentrations can be hundreds of times greater than whole blood or plasma concentrations [13].

In contrast to COVID-19, malaria is principally an infection of red blood cells. Thus, pharmacokinetic sampling of the peripheral blood constitutes a tissue biopsy in malaria and therein provides a direct marker of the target compartment rather than a dubious stand-in. Despite this, in more than half a century of research, studies of HCQ have found little to no correlation between drug concentrations and therapeutic response in malaria, and the same is true for rheumatologic diseases [14–16].

In addition to its abstruse pharmacokinetics, too little is known about HCQ pharmacodynamics to guide an appropriate dose optimization study design in COVID-19. The mechanism of HCQ's antiviral activity, if any, has not been elucidated. Also unknown are the pharmacokinetic/pharmacodynamic relationships between HCQ and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of COVID-19, or between HCQ and the systemic inflammatory response, should it be the case that HCQ exerts a therapeutic effect by modulating host immunity. The site of therapeutic action, if any, probably resides in the intracellular compartment, but intracellular concentrations have little to no discernable relationship to peripheral blood concentrations of HCQ [13].

If there were a clinically significant benefit of HCQ in COVID-19, is it concentration- or time-dependent? New models that account for target tissue pharmacokinetics suggest that HCQ regimens currently in clinical use and studied in clinical trials, some which approach safe dosing limits, may not reach maximal effect [17]. If those models hold, it would imply a narrow therapeutic window, all the more reason for exercising caution in moving forward with HCQ for COVID-19. Although less toxic than its predecessor CQ by design, serious neuro- and cardiotoxicities have been documented when HCQ plasma concentrations reach the range of 640–9870 ng/mL [18].

In the end, the authors conclude that additional pharmacokinetic studies are warranted to optimize HCQ dosing for COVID-19. Perinel et al recommend therapeutic drug monitoring to tailor patient regimens and further work to define HCQ's antiviral effects. Martin-Blondel et al also make an interesting appeal to monitor HCQ concentrations in bronchoalveolar lavage fluid. Incidentally, bronchoalveolar lavage is suboptimal for pharmacokinetic studies for a number of reasons, including its variable dilution and analytical challenges posed by nonstandard matrices.

More than a century ago, the grandfather of clinical pharmacology, Rudolph Bucheim, wryly observed that "a surgeon who uses the wrong side of the scalpel cuts [their] own fingers and not the patient; if the same applied to drugs they would have been investigated very carefully a long time ago." Despite generations of careful investigation, HCQ continues to evade easy study. Even under the best of circumstances, peripheral blood concentrations of HCQ are nearly impossible to interpret, and seeking therapeutically meaningful target concentrations is almost certainly bound to lead nowhere. Perhaps the lack of consensus around HCQ dosing strategies in ongoing clinical trials that motivated these 2 studies is for the best. If HCQ were to prove effective for COVID-19, we might arrive empirically at an optimized dosing regimen, which is likely to simply be the lowest effective dose.

Notes

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