The effect of altered PK/PD parameters on adverse drug reactions in critically ill patients with COVID-19

Mimi Tang[1], Ting Liu[1], Ping Wang[1], Xiaoping Chen[2,3,*]

[1]Department of Pharmacy, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China

[2]Department of Clinical Pharmacology, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China

[3]Institute of Clinical Pharmacology, Central South University, Hunan Key Laboratory of Pharmacogenetics, Changsha 410078, Hunan, China

[*]**Correspondence:** Xiaoping Chen (chenxiaoping@csu.edu.cn)

Abstract

Purpose Although many therapies have been proposed, there is no evidence of any effective treatment for COVID-19 to date. Currently, the main therapies being used to treat the patients with COVID-19 are cloroquine/hydroxychloroquine (+/- azithromycin), antiviral drugs (such as lopinavir/ritonavir, remdesivir, umifenovir, favipiravir), and immunomodulators (such as tocilizumab, interferon-β-1a). Pharmacokinetics (PK) and pharmacodynamics (PD) play an important role in different clinical situations, and are keys to balance the effect (reduction of SARS-CoV-2 virus and symptom improvement) and toxicity (adverse effects). However, critical patients always have altered PK and PD due to multiple factors, which might reduce or enhance the effect of drugs, and further lead to reduced efficacy or increased incidence of adverse drug reactions respectively. The purpose of present study was to understand the effects of altered PK and PD on treatment effect of drugs in critically patients with COVID-19.

Methods We used ("COVID-19" OR "2019-nCoV" OR "coronavirus" OR "SARS-CoV-2") AND ("pharmacokinetics" OR "pharmacodynamics") AND ("critical care" OR "critical illness" OR "intensive care units") AND ("treatment" OR "CRRT" OR

"ECOM" OR "plasma exchange") to perform electronic searches of the English-language literatures in online databases (PubMed, Google Scholar, MEDLINE, UpToDate, Embase and Web of Science). The search was also performed for each antimicrobial (e. g. antiviral, chloroquine/hydroxychloroquine, azithromycin).

Results Critically patients always have altered PK and PD due to multiple factors such as capillary leakage, hypoproteinemia, organ dysfunction, and organ support treatment including Mechanical ventilation, continuous renal replacement therapy (CRRT), and extracorporeal membrane oxygenation (ECMO). Meanwhile, the effects of drug interactions on drug PK/PD should also be considered. In a word, the drug dosage of antimicrobials should be adjusted according to the characteristics of the drug, such as lipidophilia, Vd, PB, metabolism, organ scavenging, and the state of patients. Generally, there is no need to adjust the dose when patients use lipophilic drugs with high Vd or low PB. However, when hydrophilic drugs with low Vd are used, the disease status has a greater impact on the distribution of drugs, and the dosage should be adjusted or maintained according to the situation. Many factors might affect the PK/PD of severe patients, and further result in large individual differences.

Conclusions Urgent research is needed to identify therapeutic targets of patient benefit and to also ascertain whether antiviral TDM is indeed meritorious in critically ill patients. Nevertheless, therapeutic drug concentration monitoring is the basis and premise of drug adjustment, and should be implemented as far as possible, which will be more conducive to the formulation of patients' precision-individual plan.

Keywords: Pharmacokinetics; Pharmacodynamics; Clinical treatments; Critically ill; COVID-19