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Antiviral Dosing Modification for Coronavirus Disease 2019–Infected Patients Receiving Extracorporeal Therapy

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Abstract: Previous literature regarding coronavirus disease 2019 outlined a presence of organ dysfunction including acute respiratory distress syndrome and acute kidney injury that are linked to mortality. Several patients require extracorporeal therapy. This review aims to gather available published resources including physicochemical and pharmacokinetic properties and suggests antiviral drug dosing adaptation for coronavirus disease 2019–infected critically ill patients receiving extracorporeal therapy. A literature search was performed using PubMed, clinical trial registries, and bibliographic review of textbooks and review articles. Unfortunately, no standard of pharmacologic management and recommendations of drug dosing for coronavirus disease 2019 infection for critically ill patients receiving extracorporeal therapy exist due to the limited data on pharmacokinetic and clinical studies. All available extracted data were analyzed to suggest the appropriate drug dosing adjustment. Antiviral drug dosing adjustments for critically ill patients receiving extracorporeal membrane oxygenation and continuous renal replacement therapy are presented in this review. Considering pathophysiologic changes, drug properties, and extracorporeal modalities, applying our suggestions is recommended.

Key Words: antivirals; continuous renal replacement therapy; coronavirus disease 2019; extracorporeal membrane oxygenation; extracorporeal therapy

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Presently, an acute respiratory tract infection caused by coronavirus disease 2019 (COVID-19) is still alarming. Several investigational agents including chloroquine/hydroxychloroquine, azithromycin, dexamethasone, darunavir/ritonavir, lopinavir/ritonavir, favipiravir, and remdesivir are used clinically based on early published evidence of clinical efficacy. In addition, a list of potential drug therapies for acute respiratory distress syndrome (ARDS) in COVID-19–infected patients has been intensively reviewed by Horie et al (1). A recent results reported by Randomised Evaluation of COVID-19 Therapy (RECOVERY) Collaborative group showed that dexamethasone use in patients with COVID-19 infection receiving respiratory support significantly reduced the 28-day mortality (2).

Reports from Wuhan, China, demonstrated the clinical presentation involved respiratory symptoms and radiographic evidence of pneumonia. Approximately 3–60% of the hospitalized patients with COVID-19 developed ARDS (3–5) with 1–11% requiring extracorporeal membrane oxygenation (ECMO) (5–7). However, there is no accepted standard pharmacologic management for patients

with COVID-19 and specific recommendation regarding medication dosage adjustment during the therapy. In addition, 5% received continuous renal replacement therapy (CRRT) (8). Similarly, antiviral dosage adjustment during CRRT was not mentioned.

Due to several uncertainties, we summarize the current evidence as of August 8, 2020, to provide guidance on anti-infective therapy dosing among patients receiving extracorporeal therapies. Literature search was performed in PubMed. Pharmacokinetics and physicochemical properties of anti-COVID-19 agents were collected. Due to limited data of physicochemical properties of some drugs, we calculated an octanol/water partition coefficient (calculated logP, cLogP) via ChemDraw Ultra 12.0 software based on the cLogP algorithm (9).

PATIENTS RECEIVING CRRT

Drug removal via CRRT depends on physicochemical properties and pharmacokinetic variables such as molecular weight (MW), volume of distribution (Vd), and protein binding (PB) rate. Drugs with small MW, low Vd, and PB are likely to be cleared by CRRT (10). Additionally, an effluent rate of CRRT prescription contributes significantly to extracorporeal clearance as high CRRT effluent rate (high volume) corresponds with the requirement for higher medication dosing (10, 11).

Considering drug properties (**Table 1**), the more hydrophilic agents including favipiravir and remdesivir may be removed via CRRT, especially with high intensity treatment. Taegtmeyer et al (12) reported the results from patients receiving CRRT with effluent flow rate of 3 L/hr and darunavir as the antiretroviral therapy. Darunavir clearance during CRRT was similar to patients with normal kidney function. Therefore, dosage adaptation of darunavir is not required in patients receiving CRRT.

On the contrary, favipiravir possesses small MW, low Vd, and PB. Although, it has the potential to be removed by CRRT. Favié et al (15) described in a case report of a patient requiring CRRT with effluent rate of 2 L/hr and received favipiravir treatment. Elevated Vd and elimination rates were found compared with the healthy volunteers and have led to subtherapeutic concentrations. The CRRT clearance did not significantly contribute to the total drug clearance. Despite high sieving coefficient of 1.1, less than 1% of administered favipiravir dose was removed via CRRT (15). Favipiravir dosing adjustment in patients with CRRT is not suggested. To our knowledge, there was no published clinical study of favipiravir in patients receiving CRRT. Considering elevated Vd and elimination rate, favipiravir dosing adjustment would depend on changes in pathophysiology of patients and high volume CRRT.

Remdesivir has low MW (602.58 g/mol) and is 87.9% protein bound. Since there were no published data on pharmacokinetic variables, dosing adaptation is extrapolated from the agent's physiochemical properties. Due to its size and moderate PB, it has the potential to be removed via CRRT, especially during the high intensity treatment. Therefore, the higher doses may be required.

Dexamethasone has a MW of 390 g/mol, Vd of 0.9L/kg, and moderate PB (65%). As physicochemical and pharmacokinetic properties, it could be extracted via CRRT. Furthermore, Honoré et al (16) reported the elimination by CRRT modality as sieving coefficient of 0.95. Consequently, they recommended increasing the dexamethasone daily dose by 110% per day in patients with CRRT.

Lopinavir/ritonavir has high PB and Vd; it therefore is not potentially removed by CRRT. Similarly, azithromycin pharmacokinetics of intermediate PB and high Vd make it difficult to be removed via CRRT. However, no pharmacokinetic studies of both agents in CRRT exist; there were pharmacokinetic studies of lopinavir/ritonavir and azithromycin in patients with

TABLE 1. Physicochemical Properties, Pharmacokinetic Variables, and Estimated Drug Sequestration in the Extracorporeal Membrane Oxygenation Circuit of Selected Antiviral Agents for Coronavirus Disease 2019 Infection Management (13)

Drugs	Molecular Weight (g/mol)	Protein Binding Rate (%)	Volume of Distribution	Log P (Octanol/Water Partition Coefficient)	Drug Sequestration in Extracorporeal Membrane Oxygenation Circuits[a]
Azithromycin	748.98	7–51	23 L/kg	4.04	Moderate to high
Chloroquine	319.90	60	200–800 L/kg	4.72	Moderate to high
Darunavir	547.67	95	131 L	2.89[b]	High
Dexamethasone	390.00	65	0.9 L/kg	1.8	Moderate
Favipiravir	157.10	54	15–20 L	0.72[b]	Minimal to moderate
Hydroxychloroquine	335.87	30–40	903–2,440 L	3.84 ± 0.2	Moderate to high
Lopinavir	628.80	98–99	0.88 L/kg	1.7	Moderate to high
Remdesivir	602.58	87.9	Not available	1.8[b] (prodrug); 1.65[b] (active form)	Moderate
Ritonavir	720.95	98–99	0.4–0.6 L/kg	1.2	Moderate to high

[a]Minimal, moderate, high defined as log P < 1 and PB < 30%, log P < 1 and PB< 70% or log P = 1–2 and PB 30–70% or log P > 2 and PB < 30%, log P > 2 and PB > 70%, respectively (14).

[b]Calculated log P from ChemDraw (9).

TABLE 2. Drug Dosing Suggestions of Selected Antiviral Agents of Coronavirus Disease 2019 Infection Treatment for Critically Ill Patients Receiving Continuous Renal Replacement Therapy and Extracorporeal Membrane Oxygenation

Drugs	Literature-Based Dosing Regimens (2, 20, 21)	CRRT	Extracorporeal Membrane Oxygenation
Azithromycin	500 mg on day 1 followed by 250 mg/d for the next 4 d	No dosage adjustment necessary	No dosage adjustment necessary
Chloroquine	500 mg q 12 hr × 7 d	No dosage adjustment necessary	Increased dosage may be required
Darunavir	600 mg q 12 hr with ritonavir	No dosage adjustment necessary	Increased dosage may be required and may increase up to 800 mg q 12 hr
Dexamethasone	6 mg daily × 10 d	May increase daily dose by 110%	Increased dosage may be required
Favipiravir	1,600 mg q 12 hr on day 1 followed by 600 mg q 12 hr × 7–10 d	No dosage adjustment necessary and may increase when high volume CRRT is required	No dosage adjustment necessary
Hydroxychloroquine	400 mg q 12 hr on day 1 followed by 200 mg q 12 hr × 5 d or 200 mg q 8 hr × 10 d	No dosage adjustment necessary	Increased dosage may be required
Lopinavir	400 mg q 12 hr × 14 d with ritonavir	No dosage adjustment necessary	Increased dosage may be required
Remdesivir	200 mg IV loading dose, then 100 mg IV daily for 5–10 d	No dosage adjustment necessary and may increase when high volume CRRT is required	Increased dosage may be required
Ritonavir	100 mg q 12 hr × 14 d	No dosage adjustment necessary	Increased dosage may be required

CRRT = continuous renal replacement therapy.

hemodialysis and peritoneal dialysis available, respectively. Both dialysis modalities contributed less effect on lopinavir/ritonavir and azithromycin removal (17, 18). Although chloroquine and hydroxychloroquine are not potentially excreted via CRRT due to high Vd, there was only one pharmacokinetic study of chloroquine in hemodialysis patients published. Chloroquine hemodialysis clearance was only 14.5% compared with total body clearance in normal patients (19). We suggest no dosage adaptation required in lopinavir/ritonavir, azithromycin, chloroquine, and hydroxychloroquine for patients receiving CRRT. Potential antiviral dosing adaptation during CRRT was suggested in **Table 2**.

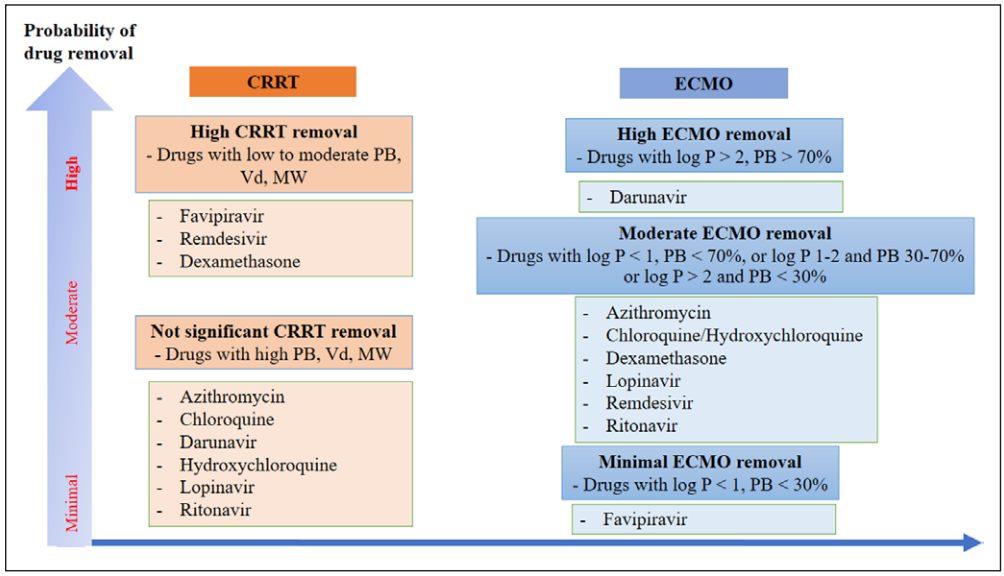

Figure 1. Probability of drug removal via extracorporeal therapy based on physicochemical properties and pharmacokinetic variables. CRRT = continuous renal replacement therapy, ECMO = extracorporeal membrane oxygenation, MW = molecular weight, PB = protein binding, Vd = volume of distribution.

PATIENTS RECEIVING ECMO

The ECMO circuits have large surface areas due to membrane oxygenator, conduit tubing, and other circuit components. Drugs can be bound into membrane surfaces and consequently increasing Vd (14, 22). Furthermore, hemodilution from a large volume of priming fluid and physiologic changes related to severe illness can also increase Vd. These factors may decrease drug concentrations (14, 22). Generally, the drug lipophilicity is defined by logP. Drugs with higher logP values confer higher lipophilicity. Lipophilic drugs tend to be bound in the ECMO circuits comparing with hydrophilic agents due to the higher solubility in the circuit. In addition, drugs with the high PB are lost in the circuit due to drug sequestration despite similar lipophilicity. Therefore, the lipophilicity and PB are mainly considered for dosage adjustment during ECMO therapy (14). Applying

physicochemical and pharmacokinetic variables, antiviral drugs can be classified as minimal, moderate and high possibilities to be sequestrated in the ECMO circuits.

Darunavir (high logP, PB) has high possibility of drug lost in the circuit, whereas ritonavir has the moderate to high probability to be sequestrated due to the high PB and moderate logP. Based on the results from the study by Ghazi Suliman et al (23), the concentrations were observed in an expected range based on the model prediction while darunavir concentrations showed higher than the expected values for a typical individual with the regimen of 800 mg every 12 hours during the ECMO therapy. They suggested that the aggressive darunavir/ritonavir regimen of 800/100 mg every 12 hours as an antiretroviral therapy was appropriate in patients requiring the ECMO (23). We recommend not adjusting the darunavir/ritonavir dosing regimens as recommended for the COVID-19 but may increase the dose up to 800/100 mg every 12 hours as needed.

Lopinavir/ritonavir, chloroquine/hydroxychloroquine, and azithromycin shared similar properties and have moderate to high possibilities to be lost in the circuit. Unfortunately, no pharmacokinetic study to aid dosing adjustment exists. We recommend that dosing adaptation may be required for these agents based on physicochemical and pharmacokinetic properties. However, there was a pharmacokinetic study of azithromycin conducted in three patients with ARDS and receiving the ECMO (24). Azithromycin pharmacokinetic variables were calculated using noncompartmental analysis and then compared those values in terms of Vd, clearance, and area under the concentration time curve with previously published reports in non-ECMO patients. The ECMO therapy did not substantially affect azithromycin pharmacokinetics (24). Consequently, dosing adjustment of azithromycin in patients with the ECMO is not required.

Favipiravir is more hydrophilic due to its logP, has low PB and Vd. It was classified as the minimal to moderate possibility to be lost in the ECMO circuits. Similarly, there were no published pharmacokinetic data in patients with the ECMO available. Use of normal favipiravir dose was recommended in these patients, and the higher doses might be applied in critically ill patients with extremely high fluid accumulation.

Dexamethasone has the moderate possibility to be lost via the ECMO circuit depending on logP of 1.8 and PB of 65% (16, 25). Owing to no pharmacokinetic studies of dexamethasone in patients receiving ECMO exists, standard dexamethasone dosing regimens based on the clinical study should be prescribed.

Remdesivir was classified to have the moderate possibility to be lost via the ECMO circuit due to a calculated logP of active drug and PB. Standard dosing regimens should be encouraged until published pharmacokinetic and clinical studies are available.

Based on physicochemical properties and pharmacokinetic data of antiviral agents, we illustrated the probability of drug removal via CRRT and ECMO in **Figure 1**.

As mentioned, there were only darunavir, favipiravir, and azithromycin pharmacokinetic studies conducted and published in critically ill patients receiving CRRT and ECMO to aid drug dosing. Additionally, given no antiviral agents have been approved for the COVID-19 infection, using these antiviral agents should be carefully considered based on updated clinical studies and FDA cautions as reported for lopinavir/ritonavir (26), chloroquine, and hydroxychloroquine (27). Furthermore, the clinical pharmacokinetic study to confirm the remdesivir dosing regimens for COVID-19–infected patients receiving extracorporeal therapy is still lacking. Extracorporeal drug removal of some agents listed in Table 2 contributes major concerns in drug dosing adaptation. Inappropriate dosing adjustment in patients with CRRT and ECMO may compromise the results of some potential drugs in clinical trials and clinical responses for treating individual patients. When antivirals are needed to be prescribed, considering drugs' physicochemical and pharmacokinetic properties and changes in pathophysiology of severely ill patients to modify drug dosing is the best alternative way to ensure the efficacy and decrease a risk of occurring toxicity. Last, pharmacokinetic evaluation of anti-COVID-19 drugs in critically ill patients with extracorporeal therapies is required.

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