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Review

Evaluating the elimination status of medications used for COVID-19 during hemoperfusion and therapeutic plasma exchange: A review

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ABSTRACT

Since late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, better known as COVID-19) has rapidly spread worldwide. The primary pathophysiology by which COVID-19 leads to severe lung damage is cytokine releasing syndrome (CRS), which can cause death. Therefore, removing cytokines via therapeutic plasma exchange or hemoperfusion could be a therapeutic approach to treat CRS. However, hemoperfusion or therapeutic plasma exchange could alter the effectiveness of concomitant medications. Thus, concomitant medication doses might need to be adjusted to prevent their elimination via therapeutic plasma exchange or hemoperfusion, thus ensuring that these medications remain effective. This narrative review investigates the elimination status of current medications used to manage COVID-19 during hemoperfusion and therapeutic plasma exchange, with a focus on their pharmacokinetic profiles.

1. Introduction

COVID-19 is a fulminant disease that is often accompanied by acute respiratory distress syndrome (ARDS), acute thrombosis, sepsis, and end-organ failure [1,2]. Different strategies have been employed to manage these conditions, with early interventions including oxygenation, coagulation modifications, antiviral and immunologic therapy.

The primary pathophysiology by which COVID-19 leads to severe lung damage—followed by death—is cytokine releasing syndrome (CRS), or cytokine storms leading to multi-organ failure (MOF) [2]. It progresses rapidly and has a high mortality rate. Therefore, the removal of cytokines via therapeutic plasma exchange (TPE) or hemoperfusion (HP) could be a viable therapeutic option for those infected by COVID-19. However, HP and TPE may significantly alter the pharmacokinetic profiles of concomitant medications that patients might be given to treat COVID-19. These medications might even be eliminated, meaning that no therapeutic benefits will be achieved.

Hence, the potential elimination of other medications that the patient receives while on TPE or HP needs to be considered. In this narrative review, we searched Pubmed, Scopus, and Web of Science databases to gather data regarding the pharmacokinetic profiles of medications prescribed to COVID-19 patients during TPE or HP. This review could help healthcare providers make better decisions regarding the timing of medication administration.

2. Hemoperfusion

HP is an extracorporeal blood purification modality that selectively removes abnormal cells, components, and cytokines in the blood due to specific disease states [3,4].

In acute inflammatory situations, such as COVID-19, hemoperfusion with HA330 cartridges effectively removes cytokines [3]. However, HP can also reduce the blood concentration of concomitant medications used to treat COVID-19. Hence, the evaluation and prediction of drug removal by HP are crucial issues.

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Table 1
The potential elimination status of the medications currently in use for COVID-19 during the therapeutic plasma exchange and hemoperfusion.

Medication	Molecular Weight	Half-life	Volume of Distribution (L/kg or L, assuming 70 kg body weight)	Plasma Protein Binding	Considerations during TPE	Considerations during HP
Tocilizumab [11,12]	148,000 Daltons	Up to 14 days	2.8–4.5 L	N/A	Significantly removable via TPE. A supplemental dose can be given after TPE to maintain the long half-life of tocilizumab. Administering tocilizumab after TPE is preferred.	Not removable
Ribavirin [13,14]	244.206 g/mol	Capsule: 24 h in healthy adults, 44 h in patients with chronic hepatitis C infection. Tablet, single-dose: ~120 to 170 h	799–2730 L or 11-39L/kg	Not bound	Probably not removable by TPE. Slow distribution and accumulation of its metabolites in erythrocytes may prevent removal via the TPE process.	Not removable
Favipiravir [15–17]	157.1 g/mol	2 to 5.5 h	15–20 L	54%	Favipiravir is suspected to be removed by TPE and its administration before the process is discouraged.	Not removable
Remdesivir [18,19]	602.6 g/mol	20 h	N/A	N/A	There is no data regarding remdesivir's pharmacokinetic and pharmacodynamic profile during TPE. As a precaution, it is better not to administer remdesivir before plasma exchange. Data in hemodialysis patients revealed its safety and efficacy.	N/A. The use of remdesivir was safe and effective in End Stage Renal Disease patients who were infected with SARS-CoV-2 and required hemodialysis.
Lopinavir/Ritonavir [20–22]	628.8/720.9 g/mol	5 to 6 h	144–244 L or 2–3.5L/kg	Approximately 98–99%. Lopinavir binds to both a_1-acid glycoprotein (AAG) and albumin, but has a higher affinity for AAG.	Lopinavir/Ritonavir may be removed by TPE and should be administered after the process.	Not removable
Atazanavir/Ritonavir [23,24]	704.9/720.9 g/mol	9 to 18 h; 12 h in patients with hepatic impairment	131 L or 1.8 L/kg	86% bound to serum proteins; binding independent of concentration. Binds to both a_1-acid glycoprotein (89%) and albumin (86%).	The pharmacokinetic characteristics make it prone to elimination via TPE. Thus, it should be administered after the completion of the process.	Not removable
Chloroquine Phosphate [25]	515.9 g/mol	Healthy subjects: 74.7 ± 30.1 h. Chronic renal insufficiency: 191.4 ± 69.1 h (range: 103.5 to 309.9 h)	113 L/kg or 8000–13000 L	55%	It seems that TPE does not have a significant impact on the removal of chloroquine phosphate due to a huge V_d (113L/kg) and 55% capacity to bind to plasma proteins.	Not removable
Hydroxychloroquine [25]	335.872 g/mol	~40 days	733 L and 1,630 L	40%	Owing to a low protein binding (40%) and high V_d (10.5L/kg), HCQ is not likely to be removed by TPE.	Not removable
Interferon beta-1a [26]	approximately 22,500 Daltons	19–69 h based on the route of the administration	N/A	N/A	It seems that TPE can remove interferon beta-1a. Thus, it is reasonable to administer the medication after TPE.	Removable Avonex: 95–133 hrs before HP and after HP Rebif: 345–483 h before HP and After HP
Interferon beta-1b [26]	23,000 Daltons	8 min to 4.3 h	0.25 to 2,88 L/kg	N/A	May be removed by TPE	Removable Should be administered 21.5–30.1 h before HP and after HP
IVIg [9,27,28]	300,000 Daltons	Healthy subjects: 14 to 24 days; Patients with congenital humoral immunodeficiencies: 26 to 40 days;	0.042–0.1 L/kg or 3–7.5 L	As endogenous IgG	IVIg has a low V_d and is bound to proteins. These properties suggest that IVIg is susceptible to being removed via plasma exchange.	Not removable

(*continued on next page*)

Table 1 (*continued*)

Medication	Molecular Weight	Half-life	Volume of Distribution (L/kg or L, assuming 70 kg body weight)	Plasma Protein Binding	Considerations during TPE	Considerations during HP
					Therefore, it should not be administered before TPE.	
Dexamethasone [19,29]	392.464 g/mol	7 h after oral administration and 9 h after intravenous administration	0.95 L/Kg at steady state	77%	High protein binding and moderate V_d makes this medication less prone to removal by TPE.	Not removable
Methyl prednisolone [22,30]	374.5 g/mol	1.9 ± 0.7 h	718–913 L or 18–32 L/kg	>76%	Methylprednisolone shows relatively high protein binding (>76%). This medication shows poor removal via TPE due to its rapid extravascular tissue distribution.	Not removable

IVIg: Intravenous immunoglobulin; TPE: Therapeutic Plasma Exchange; HP: Hemoperfusion; N/A: Not Available; HCQ: Hydroxychloroquine.

3. Therapeutic plasma exchange

TPE is an extracorporeal process for removing and exchanging blood plasma directly by mechanical, immunoprecipitation, cryoprecipitation, or filtration techniques [5]. In TPE, the patient's blood is passed through an apheresis device. The filtered plasma is removed and discarded, while red blood cells are reinfused and physiologic fluids, such as plasma or albumin, are replaced [6].

Data show that TPE can impact the clinical stabilization and improvement of critically ill COVID-19 patients [7]. Moreover, TPE can also be well-tolerated without any adverse effects while reducing levels of key pro-inflammatory cytokines [7].

4. Drug removal by hemoperfusion and therapeutic plasma exchange

In addition to removing cytokines, TPE and HP can remove drugs circulating in plasma compartments. Hence, the therapeutic levels may fluctuate to subtherapeutic levels, and serum concentration levels should be measured if possible. However, to the best of our knowledge, few trials have measured the concentrations of drugs used to treat COVID-19 during TPE or HP [6,8,9].

Drug removal by TPE is a multifactorial phenomenon that can be affected by the pharmacokinetic characteristics of the drug. Several parameters that affect drug removal by TPE include plasma-protein binding, molecular weight, the volume of distribution (V_d), half-life, and extracorporeal clearance. Among all these parameters, a low volume of distribution (V_d) (i.e., <0.2 L/kg) and a high rate of protein binding (i.e., >80%) strongly affect drug removal during TPE [6,9]. Generally, medications with a volume of distribution of <0.2 L/kg or plasma protein binding of >80% are most likely to be removed during TPE [6]. It is believed that TPE might have a slight impact on drug removal when endogenous clearance is less than 4 mL/min and the drug half-life is longer than 2 h. We tried to gather information regarding these characteristics and the pharmacokinetic profiles of medications currently used to treat COVID-19. The collected data could lead to better predictions of whether a specific medication will be removed via TPE/HP (Table 1).

HP removes drugs by directly binding to the sorbent material in the adsorption cartridge containing neutro-macroporous resin adsorbing beads [4]. Several types of cartridges with a wide pore size distribution are available for various conditions. These include HA130 (pore size distribution = 500–40,000 Da) for chronic conditions, HA230 (pore size distribution = 200–10,000 Da) for intoxication, and HA330 (pore size distribution = 500–60,000 Da) for acute inflammatory conditions such as cytokine storms brought on by COVID-19 [10]. Depending on the pore size, HP can remove broad-spectrum molecular weight drugs up to 60,000 Da [4,10]. In COVID-19 (as an acute inflammatory condition), HA330 cartridges are used to reduce cytokine storms and inflammation [10].

5. Results

We attempted to practically unify existing information to prepare a framework of expected variations in plasma concentration levels of medications administered to treat COVID-19 patients undergoing TPE and HP. The findings are summarized in Table 1.

6. Discussion

The present review discusses the extant literature that has assessed the impacts of TPE and HP on different medications administered to treat COVID-19. This review recommends an appropriate time to administer medications to COVID-19 patients undergoing HP or TPE when applicable.

To date, no specific medications have been proven to have high efficacy for COVID-19. Treatments are still being investigated through clinical trials. Current medications with potential therapeutic benefits for COVID-19 include interferon beta-1a, interferon beta-1b, IVIg, ribavirin, methylprednisolone, Dexamethasone, atazanavir/ritonavir, lopinavir/ritonavir, hydroxychloroquine, chloroquine, favipiravir, and remdesivir. Moreover, TPE and HP can be considered therapeutic approaches for removing cytokines associated with severe cases of COVID-19 [3]. However, these interventions might remove concomitant medications. Hence, the potential elimination of these medications needs to be evaluated based on their pharmacokinetic profile. Such evaluations could prevent subtherapeutic concentrations of concomitant medications.

7. Conclusion

A variety of medications administered to treat COVID-19 could be removed by TPE. Therefore, it is crucial to consider this elimination and consider the proper timing for administration. The data presented in this review were gathered based on the pharmacokinetic profiles of relevant medications. More clinical trials should be conducted to confirm these results.

CRediT authorship contribution statement

Shervin Shokouhi: Conceptualization, Writing - review & editing. **Saghar Barati:** Conceptualization, Writing - review & editing. **Neda**

Kazeminia: Writing - review & editing. **Faezeh Jamali:** Writing - review & editing. **Baran Roshan:** Writing - review & editing. **Zahra Sahraei:** Conceptualization, Methodology, Writing - review & editing.

References

[1] T. Iba, et al., Coagulopathy in COVID-19, J. Thromb. Haemost. 18 (9) (2020) 2103–2109.
[2] C. Robba, et al., Multiple organ dysfunction in SARS-CoV-2: MODS-CoV-2, Exp. Rev. Respirat. Med. 14 (9) (2020) 865–868.
[3] S. Safari, et al., Extracorporeal hemoperfusion as a potential therapeutic option for severe COVID-19 patients; a narrative review, Arch. Acade. Emerg. Med. 8 (1) (2020).
[4] G. Ankawi, et al., A new series of sorbent devices for multiple clinical purposes: current evidence and future directions, Blood Purif. 47 (1–3) (2019) 94–100.
[5] E. Muirhead, A.F. Reid, A resin artificial kidney, J. Lab. Clin. Med. 33 (7) (1948) 841–844.
[6] C.W. Cheng, et al., Therapeutic plasma exchange and its impact on drug levels: an ACLPS critical review, Am. J. Clin. Pathol. 148 (3) (2017) 190–198.
[7] G. Hampel, et al., Experience with fixed-bed charcoal haemoperfusion in the treatment of severe drug intoxication, Arch. Toxicol. 45 (2) (1980) 133–141.
[8] R.B. Ibrahim, R.A. Balogun, Medications in patients treated with therapeutic plasma exchange: prescription dosage, timing, and drug overdose, in: Seminars in Dialysis. 2012. Wiley Online Library.
[9] R.B. Ibrahim, et al., Drug removal by plasmapheresis: an evidence-based review, Pharmacoth. J. Human Pharmacol. Drug Therapy 27 (11) (2007) 1529–1549.
[10] D.P. Montin, et al., Biocompatibility and cytotoxic evaluation of new sorbent cartridges for blood hemoperfusion, BloodPurif. 46 (3) (2018) 187–195.
[11] H. Abdallah, et al., Pharmacokinetic and pharmacodynamic analysis of subcutaneous tocilizumab in patients with rheumatoid arthritis from 2 randomized, controlled trials: SUMMACTA and BREVACTA, J. Clin. Pharmacol. 57 (4) (2017) 459–468.
[12] X. Zhang, R. Peck, Clinical pharmacology of tocilizumab for the treatment of patients with rheumatoid arthritis, Expert Rev. Clin. Pharmacol. 4 (5) (2011) 539–558.
[13] R.G. Gish, Treating HCV with ribavirin analogues and ribavirin-like molecules, J. Antimicrob. Chemother. 57 (1) (2006) 8–13.
[14] P. Glue, The clinical pharmacology of ribavirin, in: Seminars in liver disease, 1999.
[15] T.H.T. Nguyen, et al., Favipiravir pharmacokinetics in Ebola-Infected patients of the JIKI trial reveals concentrations lower than targeted, PLoS Neglected Tropical Diseases 11 (2) (2017), e0005389.
[16] Y.X. Du, X.P. Chen, Favipiravir: pharmacokinetics and concerns about clinical trials for 2019-nCoV infection, Clin. Pharmacol. Ther. (2020).
[17] S. Joshi, et al., Role of favipiravir in the treatment of COVID-19, Int. J. Infect. Diseases (2020).
[18] J.C. O'Horo, Remdesivir, Elsevier, 2020.
[19] D. Aiswarya, et al., Use of Remdesivir in patients with Covid-19 on hemodialysis – a study of safety and tolerance, Kidney Int Rep (2020).
[20] C. Klein, et al., Population pharmacokinetic/pharmacodynamic analyses of lopinavir and ritonavir in subjects receiving the tablet formulation, HIV 9 (2008) 9–13.
[21] N.A. Qazi, A.L. Pozniak, J.F. Morlese, Lopinavir/ritonavir (ABT-378/r), Expert Opin. Pharmacother. 3 (3) (2002) 315–327.
[22] Medicine, N.L.o. and N.C.f.B. Information. pubchem. 2005 2021.
[23] F. Foissac, et al., Population pharmacokinetics of atazanavir/ritonavir in HIV-1-infected children and adolescents, Br. J. Clin. Pharmacol. 72 (6) (2011) 940–947.
[24] Veerabhadram, G., Subramanyam, C., Vejendla, R., 2017. RP-HPLC METHOD DEVELOPMENT AND VALIDATION FOR SIMULTANEOUS ESTIMATION OF COBICISTAT AND ATAZANAVIR IN BULK AND PHARMACEUTICAL DOSAGE FORM. 2017.
[25] M.R. Nicol, et al., Pharmacokinetics and pharmacological properties of chloroquine and hydroxychloroquine in the context of COVID-19 infection, Clin. Pharmacol. Ther. 108 (6) (2020) 1135–1149.
[26] R.J. Wills, Clinical pharmacokinetics of interferons, Clin. Pharmacokinet. 19 (5) (1990) 390–399.
[27] T. Koleba, M.H. Ensom, Pharmacokinetics of intravenous immunoglobulin: a systematic review, Pharmacotherapy: J. Human Pharmacol. DrugTherapy 26 (6) (2006) 813–827.
[28] H. Kessary-Shoham, et al., In vivo administration of intravenous immunoglobulin (IVIg) can lead to enhanced erythrocyte sequestration, J. Autoimmun. 13 (1) (1999) 129–135.
[29] N.A. Al Katheeri, et al., Pharmacokinetics and pharmacodynamics of dexamethasone after intravenous administration in camels: effect of dose, Vet. Res. Commun. 28 (6) (2004) 525–542.
[30] S. Szefler, et al., Methylprednisolone versus prednisolone pharmacokinetics in relation to dose in adults, Eur. J. Clin. Pharmacol. 30 (3) (1986) 323–329.