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SHORT REPORT

Hemoadsorption eliminates remdesivir from the circulation: Implications for the treatment of COVID-19

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Abstract

Both antiviral treatment with remdesivir and hemoadsorption using a CytoSorb® adsorption device are applied in the treatment of severe COVID-19. The CytoSorb® adsorber consists of porous polymer beads that adsorb a broad range of molecules, including cytokines but also several therapeutic drugs. In this study, we evaluated whether remdesivir and its main active metabolite GS-441524 would be adsorbed by CytoSorb®. Serum containing remdesivir or GS-441524 was circulated in a custom-made system containing a CytoSorb® device. Concentrations of remdesivir and GS-441524 before and after the adsorber were analyzed by liquid chromatography-tandem mass spectrometry. Measurements of remdesivir in the outgoing tube after the adsorber indicated almost complete removal of remdesivir by the device. In the reservoir, concentration of remdesivir showed an exponential decay and was not longer detectable after 60 mins. GS-441524 showed a similar exponential decay but, unlike remdesivir, it reached an adsorption–desorption equilibrium at ~48 µg/L. Remdesivir and its main active metabolite GS-441524 are rapidly eliminated from the perfusate by the CytoSorb® adsorber device *in vitro*. This should be considered in patients for whom both therapies are indicated, and simultaneous application should be avoided. In general, plasma levels of therapeutic drugs should be closely monitored under concurrent CytoSorb® therapy.

KEYWORDS
COVID-19, cytokine, hemoadsorption, remdesivir, SARS-CoV-2

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Alexander Supady and Achim Lother contributed equally.

1 | INTRODUCTION

In humans, infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), which can lead, in severe cases, to excessive inflammation and ultimately to life-threatening pneumonia. Antiviral treatment with remdesivir, a nucleoside analogue hampering the viral RNA polymerase, was recommended for hospitalized patients with severe COVID-19.[1,2] Beyond this, extracorporeal cytokine adsorption using a CytoSorb® adsorption device (CytoSorbents Corp., Monmouth Junction, New Jersey, USA) was suggested for mitigation of excessive inflammatory response in COVID-19.[3] The CytoSorb® adsorber consists of porous polymer beads that adsorb molecules within the 5–55 kDa range, including cytokines, myoglobin, or bilirubin, but also therapeutic drugs.[4] It can be integrated in extracorporeal membrane oxygenation systems or continuous renal replacement therapy circuits and is used for different indications, including intoxications, rhabdomyolysis, liver failure, or septic shock.[4] Recently, the United States Food and Drug Administration has authorized the emergency use of the CytoSorb® adsorber for the treatment of COVID-19[5] but there are no data available on potential interaction with remdesivir use. Thus, the aim of this study was to investigate whether remdesivir would be adsorbed by CytoSorb®.

2 | MATERIAL AND METHODS

Remdesivir is a prodrug that is rapidly metabolized in humans to its main active metabolite GS-441524.[6] To evaluate the capacity of the CytoSorb® hemoadsorption device to eliminate remdesivir or GS-441524, we applied a previously published protocol.[7,8] A CytoSorb® device was integrated in a custom-made system using a peristaltic pump (AlphaControl PSP-V12G, Figure 1) and primed with fetal calf serum (Sigma-Aldrich, Taufkirchen, Germany). Remdesivir (1200 µg/L) or GS-441524 (200 µg/L, both Cayman Chemical, Ann Arbor, MI, USA) at concentrations similar to plasma levels observed in humans[6] was dissolved in 2,000 mL serum supplemented with NaF (2.5 g/L) for stabilization. The solutions were circulated from a reservoir at a flow rate of 200 mL/min for 60 mins at 36.5°C in two separate experiments. Samples (1 mL) were taken from the circuit simultaneously before (pre) and after (post) the adsorption device at 0, 5, 10, 15, 30, and 60 mins (Figure 1). The adsorption device was replaced after each experiment. Concentrations of remdesivir (linearity 25–1000 ng/mL, limit of detection 0.54 ng/mL, limit of quantification 1.1 ng/mL) and GS-441524 (linearity 2.5–100 ng/mL, limit of detection 0.82 ng/mL, limit of quantification 0.84 ng/mL) were analyzed within 4 h by

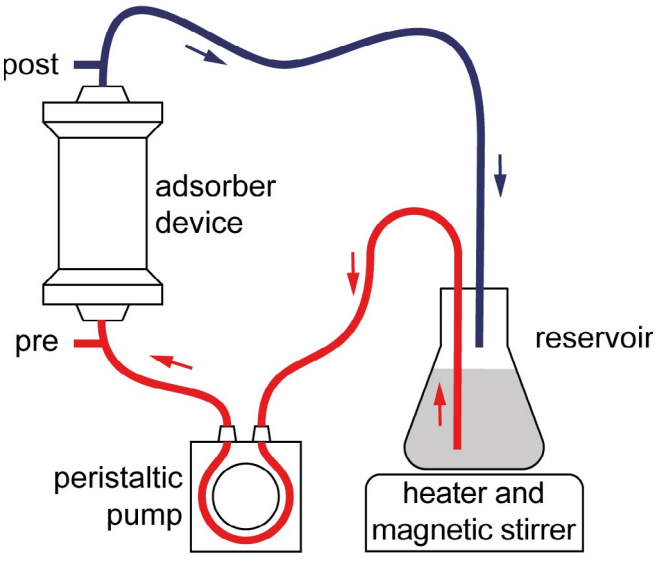

FIGURE 1 Experimental setup. A CytoSorb® device was integrated in a custom-made system, and serum containing remdesivir or GS-441524, respectively, was circulated from a reservoir at a flow rate of 200 mL/min. Samples were taken from the circuit before (pre) and after (post) the adsorber device at 0, 5, 10, 15, 30, and 60 minutes for quantification of remdesivir or GS-441524

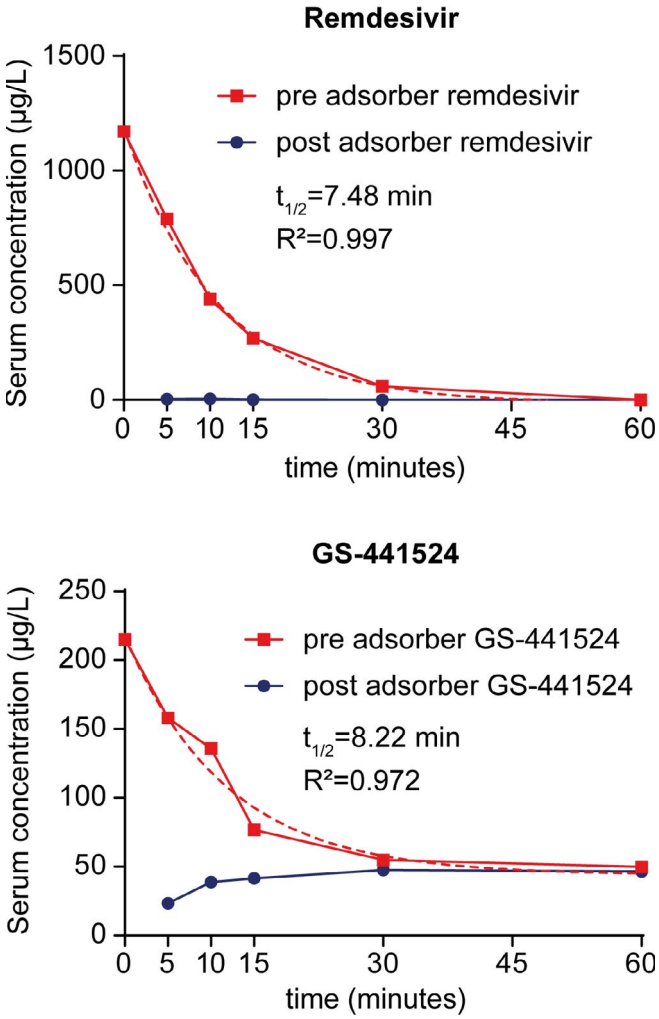

FIGURE 2 Adsorption of remdesivir or GS-441524 *in vitro*. Concentrations of remdesivir or GS-441524 in samples taken from the circuit before (pre) and after (post) the adsorber device were quantified by liquid chromatography with mass spectrometry detection. Dashed lines indicate calculated half-life ($t_{1/2}$)

TABLE 1 Removal of therapeutic drugs by the CytoSorb® adsorption device *in vitro*

Compound (PubChem ID)	Compound class	Molecular weight (g/mol)	Plasma protein binding	Water solubility	Adsorption in vitro	Ref.
Gentamicin (3467)	Aminoglycoside antibiotic	477.6	Low	Soluble	Poor	[8]
Amikacin (37768)	Aminoglycoside antibiotic	585.6	Low	Soluble	Poor	[8]
Netilmicin (441306)	Aminoglycoside antibiotic	475.6	Low	Soluble	Poor	[8]
Tobramycin (36294)	Aminoglycoside antibiotic	467.5	Low	Soluble	Poor	[8]
Phenytoin (1775)	Hydantoin derivate antiepileptic	252.3	High	Insoluble	Poor	[8]
Phenobarbital (4763)	Barbituric acid derivate	232.2	Moderate	Low	Moderate	[8]
Vancomycin (14969)	Glycopeptide antibiotic	1449.2	Moderate	Soluble	Significant	[8]
Teicoplanin (133065662)	Glycopeptide antibiotic	1879.7	High	Soluble	Significant	[8]
Digoxin (2724385)	Cardiac glycoside	780.9	Low	Low	Significant	[8]
Carbamazepine (2554)	Dibenzoazepine antiepileptic	236.3	High	Low	Significant	[8]
Valproic acid (3121)	Propylpentanoic acid derivate antiepileptic	144.2	High	Low	Significant	[8]
Theophylline (2153)	Xanthine derivative	180.2	Moderate	Low	Significant	[8]
Tacrolimus (445643)	Macrolide derivate	804.0	High	Insoluble	Significant	[8]
Everolimus (6442177)	Macrolide derivate	958.2	High	Low	Significant	[8]
Dabigatran (216210)	Thrombin inhibitor	471.5	Low	Low	Significant	[12]
Edoxaban (10280735)	Factor Xa inhibitor	548.1	Moderate	Low	Significant	[13]
Rivaroxaban (9875401)	Factor Xa inhibitor	435.9	High	Insoluble	Significant	[14]
Ticagrelor (9871419)	Adenosine nucleotide analogue platelet inhibitor	522.6	High	Low	Significant	[15]
Remdesivir (121304016)	Adenosine nucleotide analogue antiviral	602.6	Moderate to high	Insoluble	Significant	Biever et al
GS-441524 (44468216)	Adenosine nucleotide analogue antiviral	291.3	Low	Insoluble	Significant	Biever et al

Note: Chemical properties were derived from PubChem database (https://pubchem.ncbi.nlm.nih.gov).

a liquid chromatography-tandem mass spectrometry method after protein precipitation using D4-remdesivir as internal standard (modified after[9]). Half-lives were calculated by a one-phase exponential decay model (Y = (Y0-NS)*exp(−K*X) + NS) using GraphPad Prism 9.0.0.

3 | RESULTS

At 5, 10, 15, and 30 mins, concentrations of remdesivir in the outgoing tube after the adsorber were below 1% of the pre-adsorber concentration, indicating almost complete removal of remdesivir by the device. In line with that, serial measurements revealed a one-phase exponential decay of remdesivir in the reservoir with a calculated half-life of 7.48 minutes (R^2 = .997). After 60 mins, remdesivir was not longer detectable (Figure 2). GS-441524 showed a similar exponential decay with a calculated half-life of 8.22 mins (R^2 = .972) but, unlike remdesivir, it was not completely removed. We observed an increase in the post-adsorber concentration of GS-441524, starting at 5 mins and reaching adsorption–desorption equilibrium at 60 mins (before 49.8 µg/L and after 46.6 µg/L; Figure 2).

4 | DISCUSSION

Our results show that remdesivir and GS-441524 are rapidly eliminated from the perfusate by the CytoSorb® adsorption device in an *in vitro* model. These observations should be considered when treating COVID-19 patients with cytokine adsorption and remdesivir.

While remdesivir is rapidly metabolized, its main active metabolite GS-441524 has a long plasma half-life of ~24.5 h in humans.[6] Though metabolism of remdesivir in vivo is complex, our results suggest that concurrent adsorption therapy with CytoSorb® could significantly limit systemic exposure and thus antiviral effectiveness of GS-441524. We observed a saturation plateau of GS-441524 at ~48 ng/ml (~0.16 µM), which might be explained by a lower affinity to the adsorber of GS-441524 compared to remdesivir. The remaining circulating levels were significantly below the effective antiviral concentration of GS-441524 against SARS-CoV-2 (EC-50 0.47 - 1.09 µM) that has been determined in vitro.[10]

The prognostic value of both, remdesivir and hemoadsorption, in the treatment of COVID-19 is still under investigation. While a benefit of early use of remdesivir in hospitalized patients with severe symptoms is plausible, the benefit in later disease stages remains questionable at

this time.[1,2] In contrast, hemoadsorption therapy may be limited to critical cases of COVID-19 that are associated with a significant increase in cytokine levels. This, however, remains to be confirmed.[3]

Possible interactions of different treatment regimen in COVID-19 demand careful consideration. This is particularly true for antiviral drugs, for which significant drug–drug interactions have been described,[11] but also includes non-pharmacological therapies. Our data suggest that concurrent use of remdesivir and hemoadsorption should rather be avoided and support the view that sequential use at different stages of COVID-19 may be preferred. The results presented here complement previous reports describing desired or unwanted adsorption of various molecules by the CytoSorb® device.[7,8,12-15] In vitro data are available on a broad range of therapeutic drugs that are commonly used in intensive care medicine (Table 1). Drugs that are adsorbed differ in molecule size, solubility, and protein binding, making it difficult to make predictions about a particular substance. Therefore, the influence of hemoadsorption therapy on therapeutic drugs should be systematically assessed in vivo and closely monitored during clinical application.

In summary, remdesivir and its main active metabolite GS-441524 are rapidly eliminated from the perfusate by the CytoSorb® adsorber device *in vitro*. This should be considered in COVID-19 patients for whom both therapies are indicated, simultaneous application should rather be avoided. Plasma levels of therapeutic drugs should be closely monitored under concurrent CytoSorb® therapy.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Paul Biever, Dawid L. Staudacher, Merja A. Neukamm, Christoph Bode, Alexander Supady, and Achim Lother contributed to conception and design of the study and interpreted data. Michaela J. Sommer, Hannah Triebel, and Achim Lother performed experiments, and acquired and analyzed data. Paul Biever, Dawid L. Staudacher, Alexander Supady, and Achim Lother drafted the manuscript. Michaela J. Sommer, Hannah Triebel, Merja A. Neukamm, and Christoph Bode revised the manuscript. All authors gave final approval of the version to be published.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

ETHICS STATEMENT

Not applicable.

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