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Mechanistic Considerations and Pharmacokinetic Implications on Concomitant Drug Administration During CytoSorb Therapy

Joerg Scheier, MD[1]
Peter J. Nelson, MD, FASN[2]
Antoine Schneider, MD, PhD[3–4]
Sébastien Colombier, MD[5]
Detlef Kindgen-Milles, MD, PhD[6]
Efthymios N. Deliargyris, MD, FACC, FESC, FSCAI[2]
Thomas D. Nolin, PharmD, PhD[7]

OBJECTIVE: The CytoSorb hemoadsorption device (CytoSorbents Inc, Monmouth Junction, NJ) is increasingly used in many critical disease states. The potential impact on the pharmacokinetic (PK) of concomitantly administered drugs must be considered in clinical practice. The current review summarizes relevant mechanistic principles, available preclinical and clinical data, and provides general guidance for the management of concomitant drug administration during CytoSorb therapy.

DATA SOURCES: Detailed search strategy using the PubMed and OVID MEDLINE databases, as well as presented congress abstracts for studies on drug removal by the CytoSorb device.

STUDY SELECTION: Human, animal, and bench-top studies with PK or drug-removal data during CytoSorb therapy were selected for inclusion. Publications reporting on CytoSorb treatments for drug overdose were not considered.

DATA EXTRACTION: Relevant PK data were examined and synthesized for narrative review.

DATA SYNTHESIS: To date, PK data during CytoSorb hemoadsorption are available for more than 50 drugs, including analgesics, antiarrhythmics, anticonvulsants, antidepressants, antihypertensives, antiinfectives, antithrombotics, anxiolytics, and immunosuppressants. Based on available PK data, drugs were categorized into low (<30%), moderate (30–60%), or high rates of removal (>60%), or, alternatively, according to clearance increase relative to endogenous clearance: negligible (<25%), low (25–100%), moderate (100–400%), or high (>400%). In most reports, additional impact of the extracorporeal platform where CytoSorb was integrated was not available. Based on available data and considering drug, patient, and setup-specific aspects, general dosing guidance for clinical practice was developed.

CONCLUSIONS: CytoSorb therapy may increase drug elimination through active removal. However, the extent of removal is heterogeneous, and its clinical significance, if any, depends on the broader clinical context, including a patient's specific endogenous drug clearance and the underlying extracorporeal platform used. The available data, although not definitive, allow for general guidance on dosing adjustments during CytoSorb therapy; however, any treatment decisions should always be complemented by clinical judgment and therapeutic drug monitoring, when available.

KEY WORDS: CytoSorb; device; drug; hemoadsorption; hemoperfusion; pharmacodynamic; pharmacokinetic

Drug removal is an important consideration in patients receiving extracorporeal therapies and may have important clinical implications in these patients as pharmacokinetic (PK)-pharmacodynamic (PD) relationships usually characterized in healthy patients may be altered in critical illness.

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Therefore, a detailed understanding of the underlying mechanisms by which a device within an extracorporeal platform might alter a drug's pharmacokinetics is paramount for appropriate dosing strategies. However, for many extracorporeal platforms used today, such data are incomplete, posing an additional challenge when CytoSorb is also integrated into these platforms. In specific clinical circumstances, drug removal is desirable. For example, CytoSorb (CytoSorbents Inc, Monmouth Junction, NJ) can efficiently remove ticagrelor and rivaroxaban intraoperatively when the device is integrated into the cardiopulmonary bypass (CPB) platform during urgent cardiac surgery, a limited short-term use of the device, in order to prevent severe perioperative bleeding (1). In other cases, however, unintended drug removal may occur during prolonged use of the device in continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO) platforms in critically ill patients.

To our knowledge, the available in vitro and in vivo data on CytoSorb's effect on PK of concomitantly administered drugs represent the largest—yet still incomplete—such data set for an extracorporeal device outside of renal replacement therapy. This comprehensive review describes relevant pharmacologic principles, summarizes the available data, and—to the best of our ability—provides practical considerations to guide clinicians in drug dosing under CytoSorb therapy at the bedside.

CYTOSORB DEVICE

The CytoSorb device is a biocompatible sorbent bead-filled hemoadsorption cartridge with adsorptive properties for predominantly hydrophobic substances with molecular weight of up to approximately 60 kDa (**Supplemental Fig. 1**, http://links.lww.com/CCX/A984). The cartridge can easily be integrated into intermittent hemodialysis or CRRT, ECMO, and CPB extracorporeal circuits, or as a stand-alone therapy in hemoperfusion mode (2).

The CytoSorb device has been approved in the European Union under Conformite Europeenne (CE) mark and labeled to remove cytokines, myoglobin, bilirubin, and the antithrombotic drugs ticagrelor and rivaroxaban from blood. It is increasingly used in more than 70 countries for these indications in a wide range of critical illnesses (2), including COVID-19 (3). Currently, CytoSorb is being used in the United States under emergency use authorization issued by the Food and Drug Administration for the reduction in proinflammatory cytokines in adult COVID-19 patients admitted to the ICU with imminent or confirmed respiratory failure (4).

The sorbent beads in the CytoSorb device can also bind drugs, especially those small, hydrophobic ones. Such drugs may then be removed from blood in a concentration-dependent fashion (**Supplemental Fig. 2**, http://links.lww.com/CCX/A984) (2). The upper molecular-weight size-exclusion of the sorbent precludes adsorption of drugs that are larger than approximately 60 kDa, for example, monoclonal antibodies. The volume of distribution (V_D) and degree of protein binding of any drug are also important factors, since only the intravascular, free (i.e., nonprotein bound) fraction of the drug can be potentially removed by CytoSorb.

METHODS

Published studies on drug removal by the CytoSorb device were identified by detailed search of the PubMed and OVID MEDLINE databases. Data from abstracts on the topic were also included in the analysis. In vitro–controlled (benchtop) and in vivo–controlled (animal) experiments to characterize drug adsorption and removal by the CytoSorb device were considered along with clinical case reports and case series published with real-world CytoSorb use. For drugs where both in vitro and in vivo data were available, the in vivo data were prioritized. Similarly, relevant to in vivo data, clearance data were prioritized over other parameters. In the absence of in vivo data, the categorization is based only on in vitro data.

Although PK data derived from closed-loop benchtop experiments cannot be directly extrapolated to clinical settings, these studies do provide important information on the likelihood and extent that CytoSorb therapy may alter specific drug concentrations. In most reports in which CytoSorb was integrated into another extracorporeal platform (e.g., CPB, CRRT, and ECMO), PK data on the effect of the extracorporeal platform apart from CytoSorb were not provided. Nevertheless, for drugs with low in vitro removal, the expected in vivo impact would also likely be minimal. On the other hand, high in vitro drug removal does not necessarily translate into clinically relevant drug

removal in vivo due to the multitude of additional factors at play including the drug's V_D and the endogenous renal and nonrenal clearances (**Supplemental Table 1**, http://links.lww.com/CCX/A983).

Typically, a substance is considered dialyzable if clearance, due specifically to the extracorporeal therapy, represents greater than or equal to 30% of total systemic clearance (5). Conversely, if extracorporeal clearance of the substance represents less than 30% of total systemic clearance, then, generally, it is considered minimally/negligibly dialyzable. Historically, this approach has been applied to drug dosing during dialytic therapies including CRRT and intermittent hemodialysis. Considering available in vitro and in vivo data, drugs studied for hemoadsorption by the CytoSorb device were categorized using similar cutoffs into low (<30%), moderate (30–60%), or high (>60%) removal potential. When available, data related to CytoSorb's impact on overall clearance were also classified according to the extent of clearance increase compared with endogenous clearance: negligible (<25%), low (25–100%), moderate (100–400%), or high (>400%), following the guidance of the European Medicines Agency on investigation of drug interactions (6).

CONSIDERATIONS FOR THE INTERPRETATION OF AVAILABLE PHARMACOKINETIC DATA

For a number of drugs, available data suggest that dose adaptations are likely not required. More specifically, CytoSorb adsorption is low for several anti-infective drugs, defined here as low in vivo percentage removal (<30%) or a negligible increase in total clearance (<25%), and dose adjustments are likely not warranted. These drugs are presented in **Table 1** and include anidulafungin, cefepime, ceftriaxone, ciprofloxacin, clarithromycin, clindamycin, flucloxacillin, ganciclovir, meropenem, metronidazole, and piperacillin. A recently published investigation confirmed the absence of clinically relevant removal of meropenem by CytoSorb in patients with sepsis or septic shock (28).

For some drugs, however, drug- and patient-specific factors, as well as the respective clinical scenario, including the potential contribution of the extracorporeal platform used to administer CytoSorb treatment, need to be taken into account for proper interpretation of the available data and derivation of clinical guidance on dosing adaptations, as outlined below.

TABLE 1.
Classification of Drugs According to Clinical Significance of CytoSorb Adsorption

Insignificant In Vivo Removal		Low In Vitro Removal	Moderate or High In Vitro Removal		Significant In Vivo Removal			
Negligible clearance increase (<25%) or low percentage removal (<30%)		<30% percentage removal but no in vivo data available	>30% percentage removal but no in vivo data available		>25% clearance increase or >30% percentage removal			
	TD	**In Vitro Data Only**		**V_D**		**TD**	**Percentage Removal (%)**	**Clearance Increase (%)**
Anidulafungin (7)	A	Amikacin (8)	Amiodarone (9)	VL	Amphotericin B (11)	A		75
Cefepime (7)	A	Paracetamol (9)	Amitriptyline (9)	VL	Bivalirudin (15)	H	> 60	
Ceftriaxone (7)	A	(Acetaminophen)	Amlodipine (11)	VL	Digitoxin (12)	H	> 60	
Ciprofloxacin (7, 13)	I, A	Theophylline (8)			Flecainide (14)	H	> 60	
Clarithromycin (7)	A		Carbamazepine (8)	L	Fluconazole (7, 13)	I, A		282

(*Continued*)

TABLE 1. (*Continued*).

Classification of Drugs According to Clinical Significance of CytoSorb Adsorption

Insignificant In Vivo Removal		Low In Vitro Removal	Moderate or High In Vitro Removal		Significant In Vivo Removal			
Clindamycin (7, 15, 16)	A, H		Cyclosporine (8, 9)	L	Linezolid (7, 17)	A, H		115
Flucloxacillin (7, 13)	I, A		Dabigatran (18)	L	Posaconazole (7)	A		32
Ganciclovir (7)	A		Diazepam (9)	L	Teicoplanin (7, 8, 19)	I, A, H		31
Meropenem (7, 13, 15, 17, 28)	I, A, H		Digoxin (8, 9)	VL	Tobramycin[a] (7, 8)	I, A		
Metronidazole (7)	A		Edoxaban (20)	L	Vancomycin (8, 10, 13, 19, 21)	I, H	>60	
Piperacillin (7, 13, 15)	I, A, H		Gentamycin (8, 13)	S	Apixaban (22)	H		
			Iodixanol (23)	S				
			Ibuprofen (9)	S				
			Phenobarbital (8)	S				
			Phenytoin (8)	S				
			Quetiapine (9)	VL				
			Remdesivir/ GS-441524 (24)	Not available				
			Rivaroxaban (25)	S				
			Tacrolimus (8, 9)	L				
			Ticagrelor (26)	L				
			Verapamil (27)	VL				
			Valproic acid (8)	S				
			Voriconazole (13)	VL				
General view on clinically expected drug removal per category, based on available data								
Unlikely to be removed to a clinically significant extent with CytoSorb therapy		Clinically significant removal by CytoSorb therapy cannot be excluded, and dose adjustments may be warranted. TDM is recommended to guide dosing wherever available	CytoSorb therapy possibly results in clinically significant removal, and dose adjustments may be warranted. TDM is recommended to guide dosing wherever available		Clinically significant removal has been demonstrated or is to be expected with CytoSorb therapy, and dose adjustments likely are warranted. TDM is recommended to guide dosing wherever availablex			

A = animal, H = human, I = in vitro, L = large >1 L/kg, S = small <1 L/kg, TD= Type of data, TDM = therapeutic drug monitoring, VD = volume of distribution (S = small <1 L/kg, L = large >1 L/kg, VL = very large >5 L/kg), provided for drugs with moderate or high in vitro removal and no in vivo data.

[a]Overall in vivo removal low, but classified here due to high initial removal and "peak concentration" nature.

DRUG PROPERTIES

Volume of Distribution

Among drug-specific aspects, the V_D is of utmost importance (29). V_D reflects the extent to which a drug distributes throughout the body. Drugs with a small V_D (<1 L/kg) tend to be mostly distributed in the intravascular fluid compartment and are, therefore, more amenable to extracorporeal removal. Drugs with large (≥1 L/kg) V_D distribute to extravascular tissues and are less accessible for extracorporeal removal. For the purpose of this review, V_D less than 1 L/kg is termed "small" V_D, V_D greater than or equal to 1–5 L/kg is termed "large" V_D, and V_D greater than 5 L/kg is termed "very large" V_D. In general, levels of drugs with large or very large V_D are less likely to be altered significantly by treatment with extracorporeal devices (5).

For drugs with moderate or high removal in vitro but with no available in vivo data on the impact of CytoSorb therapy on drug clearance, primary emphasis was put on V_D for the interpretation of percentage removal data to provide a broader view on the potential extent of drug removal to be expected under clinical conditions (Supplemental Table 1, http://links.lww.com/CCX/A983).

Protein Binding

Another drug property that can impact removal by CytoSorb is the extent of protein binding. In general, protein binding prevents distribution of drug out of the intravascular space to extravascular sites, so drugs with a high degree of binding to serum albumin (≥80%) typically exhibit a smaller V_D (30) and may be more prone to relevant total body removal through adsorption by the CytoSorb device. Adsorption by CytoSorb follows a concentration gradient between the free-fraction of the drug and the sorbent. Hence, strong protein binding limits the amount of free drug accessible for adsorption (31). Overall, the relevance of drug protein binding in the context of clinical decision-making is limited compared with other variables such as V_D.

Endogenous Clearance and Half-Life

The impact of any extracorporeal therapy on drug removal always needs to be assessed in the context of endogenous clearance and corresponding half-life of the drug. The clinical relevance of drug elimination by CytoSorb is related to the device-specific drug clearance that is added to the underlying endogenous clearance. This means that even marked drug removal by CytoSorb may not be clinically relevant for drugs with very high endogenous clearance and a corresponding short half-life (i.e., <4 hr), and likewise, even moderate-to-low elimination by an extracorporeal therapy may still need to be considered when drugs with very low endogenous clearance are in use (5).

DRUG USE

Considerations for Titratable Drugs

Functional underdosing due to possible drug removal by CytoSorb is more readily recognized with drugs that are normally titrated in real time to directly observable clinical effects. Several drugs used in anesthesiology and critical care fall into this category and include anesthetics, analgesics, sedatives, muscle relaxants, and vasoactive medications (vasopressors and inotropes). For such titratable drugs, the time of administration and mode of action are important considerations during CytoSorb therapy. For example, during intraoperative use of CytoSorb integrated into a CPB circuit, muscle relaxants administered at induction of anesthesia are already fully effective (i.e., bound to the neuromuscular receptors) at initiation of CytoSorb therapy. For these drugs, real-time assessment of drug effect using relaxometry is available and should be used.

Likewise, knowledge of the adsorptive properties for any titratable drug is important when judging whether a clinical change in a patient is due to drug removal or to evolution of the underlying disease state. To date, there is only one published report describing the need to alter dosing of titratable drugs in association with CytoSorb therapy. Specifically, the authors describe increased fentanyl requirements in COVID-19 patients on ECMO, whereas midazolam dosing on the other hand appeared to be unaffected (32). This article did not provide PK data, so inclusion of fentanyl or midazolam in Table 1 is not possible.

Time Versus Concentration Dependent Mode of Action

Different dosing strategies may be applied to drugs for which a high plasma concentration must be reached to achieve maximum effectiveness ("concentration

dependent") versus drugs requiring plasma concentrations to be maintained for a defined time frame to achieve maximum effectiveness ("time dependent"). For the first category of drugs that are "concentration dependent," it may be advisable to administer them either before CytoSorb therapy initiation or during therapy interruptions (i.e., either scheduled device exchanges or treatment pauses dedicated to drug administration) whenever possible. This category includes drugs with a very short half-life or those for which the necessity of high plasma concentrations is limited to a short time frame. Examples include antibiotics that exhibit "concentration-dependent" pharmacodynamics, like aminoglycosides (i.e., amikacin, gentamicin, and tobramycin). Initial removal by CytoSorb might decrease peak concentrations and, therefore, impact drug efficacy, whereas elimination by CytoSorb in the later course can be considered less clinically relevant. For tobramycin, the strategy of dosing during breaks in CytoSorb treatment has been proposed to allow both optimization of peak concentrations and reduction of toxicity due to subsequent removal during the early phase of CytoSorb treatment (7). As general guidance, the suggested time interval from administration of these drugs to start of CytoSorb therapy should be around 30–60 minutes, similar to the strategy suggested in patients receiving intermittent hemodialysis (33).

Conversely, for drugs exhibiting "time-dependent" pharmacodynamics, maintenance of serum concentrations above minimum concentrations until the end of the dosing interval is crucial. Examples include beta lactam antibiotics, for which animal experiments suggest transient adsorption during the first hours of CytoSorb treatment, followed by a limited desorption (i.e., drug release from the sorbent to the circulation) after a few hours. This unique effect may potentially decrease peak concentrations but may still avoid serum concentrations dropping below minimum inhibitory concentrations at the end of the dosing interval (7). For "time-dependent" drugs that are prone to relevant removal by CytoSorb, administration of an extra dose after 1–2 hours of treatment time with each new adsorber is conceptually a reasonable strategy.

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) is a crucial tool to detect and mitigate subtherapeutic dosing while avoiding overdosing in individual patients. TDM should be employed whenever possible when results can be available within a reasonable timeframe. For some drugs, monitoring of the PD effects by point-of-care tests or rapidly available laboratory tests may also be used to guide dosing. This approach allows for dose adjustments based on monitoring the drug effect instead of drug concentrations. This practical approach may be used during CytoSorb therapy and allow for any necessary dosing adjustments in real time. This is already standard clinical practice for many anticoagulant drugs like heparin or bivalirudin and may also be applicable to newer anticoagulants like dabigatran, apixaban, rivaroxaban, and edoxaban, or reversible antiplatelet agents like ticagrelor. In principle, TDM or point-of-care PD monitoring should be applied whenever available, and the availability of these monitoring tools may also play a role in the selection of applied drugs.

POTENTIAL IMPACT OF PATIENT CONDITIONS

Understanding the impact of CytoSorb therapy on drug concentrations and corresponding dosing requirements in patients also requires consideration of the high variability in PK between patients (i.e., interindividual variability in protein binding, endogenous clearance, and V_D), especially in critically ill patients on extracorporeal therapies. These patient-specific factors are likely to also impact the effect of any extracorporeal device, including CytoSorb, on drug removal. In many critical illnesses, multisystem organ dysfunction may be present, resulting in unpredictable changes in a drug's V_D, protein binding, and endogenous clearance. This may be particularly pronounced in clinical states of kidney and/or liver dysfunction, organs paramount in maintaining normal drug metabolism, fluid balance, and steady-state serum protein concentrations. Therefore, interpretation of the available data related to drug removal by CytoSorb should be considered within the specific clinical context of the patient as necessary.

CONSIDERATIONS FOR CONCOMITANTLY APPLIED EXTRACORPOREAL THERAPIES

CytoSorb therapy is delivered via integration into extracorporeal platforms (e.g., CRRT, ECMO, and CPB). In these settings, the individual contribution

from the CytoSorb device on overall drug removal may not be easily segregated from the contribution of other devices present in the parent platform (i.e., hemofilter in a CRRT circuit). Furthermore, an extracorporeal platform may itself alter a drug's V_D, protein binding, and endogenous clearance. Combined with the changes noted above in critical illness, this results in a highly complex, multifactorial state contributing to altered PK characteristics. The currently available clinical studies on drug removal by CytoSorb did not specifically discern any additional effect on PK from the parent extracorporeal platform where CytoSorb was integrated. Thus, recommendations on drug dosing during CytoSorb therapy should be contextualized with available knowledge on the effects of the parent extracorporeal platform. This topic is beyond the scope and domain of this review, and readers are referred to recent reviews on CRRT and ECMO for perspective on drug dosing when using these platforms.

DRUG DOSING CONSIDERATIONS

Drug Initiation Versus Steady-State Conditions

Drugs with a very large V_D are not likely to be impacted by extracorporeal therapies once steady-state conditions (i.e., full tissue saturation) have been achieved. Conversely, initiation of drug dosing during ongoing CytoSorb treatment may lead to more relevant drug removal than with CytoSorb treatment during steady-state conditions. If drug therapy is to be initiated during ongoing CytoSorb treatment, then higher loading doses and a supplementary dose after 1–2 hours may be advisable, although this strategy has not yet been investigated systematically.

Long-Term Versus Short-Term CytoSorb Use

In general, the extent of potential drug removal by CytoSorb also depends on the duration of exposure to the CytoSorb device. Longer exposure to CytoSorb is anticipated to lead to greater drug removal than shorter exposure within the same parent extracorporeal platform. Consequently, unintentional drug removal is considered more clinically relevant with longer term device use, for example, with serial use of several adsorbers over several days in ECMO or CRRT circuits. However, a general observation of adsorption kinetics by CytoSorb is that most of the adsorption occurs during the first few hours after installation of a new CytoSorb device, including during serial device changes. Thus, in situations where clinically relevant drug removal during CytoSorb therapy may occur, clinicians may decide to adjust the dose, taking into account the specific clinical context, by increasing the initial dose or by giving supplemental doses after the initial 1–2 hours of CytoSorb treatment and after each adsorber exchange.

Specific dosing recommendations for any drug administered during CytoSorb therapy cannot be drawn unequivocally from benchtop studies, animal studies, or clinical case reports. Notwithstanding the aspects impacting the extent of drug removal outlined so far, there are obviously a number of other clinically relevant questions in regard to more refined dosing strategies under CytoSorb in specific clinical settings. These cannot be reliably answered with the currently available limited dataset but need to be addressed in more detail in the future, based on a growing body of preferably in vivo PK data. Nevertheless, understanding the mechanistic principles impacting PK in vivo, coupled with the available data on drug removal by the CytoSorb device, can inform dosing strategies to mitigate potential adverse effects of unintentional drug removal.

In some cases, in vivo data are available ranging from animal studies to observations in critically ill patients (e.g., meropenem), whereas in other cases, the evidence informing drug dosing is derived from benchtop studies only (e.g., amikacin). Since data sources were not always consistent even among drugs belonging in the same category, some variability may be noted in the overview Table 1 (i.e., amikacin and tobramycin).

With the above important considerations in mind and with cautious interpretation of available PK data, general guidance for dose adjustment during CytoSorb therapy can be made for a variety of drugs, as suggested in Table 1.

DRUGS NOT STUDIED YET

For drugs with no available PK data during CytoSorb treatment, derivation of dosing recommendations in clinical practice is not feasible. However, as reviewed earlier, important mechanistic and PK principles including molecular weight, hydrophobicity and V_D, drug half-life, and extent of protein binding may

help determine the likelihood of significant removal. Typically, for drugs prone to removal by CytoSorb, a pattern of rapid removal during the first 1–2 hours of CytoSorb therapy, followed by a substantial decrease in removal rate for the next several hours, is observed. Conceptually, increasing the initial dose or administering a supplemental dose after 1–2 hours of CytoSorb therapy may be adequate to ensure effective drug concentrations over the course of CytoSorb therapy. However, it is important to emphasize that such recommendations that are based on the best interpretation of PK principles in combination with the available data that are frequently limited and must always take into consideration the individual clinical scenario and always defer to clinical judgment. Finally, any dosing adjustments should always be undertaken with a careful benefit:risk analysis including both the risk of subtherapeutic concentrations but also the potential for adverse effects of increased dosing.

CONCLUSIONS

Serum drug concentrations may be impacted by CytoSorb therapy. However, the extent of removal varies according to drug type and patient's clinical condition. Available PK data allow categorization of drugs according to the likelihood of removal (low, moderate, or high) and as such can inform preliminary guidance for dose adjustments during CytoSorb therapy. Importantly, the clinical significance of potential drug removal and any decisions on dosing adjustments should always be made within the broader clinical context of each patient and with the use of TDM when available.

Major Take-Home Messages and Concepts

- The possibility of unintended removal of concomitantly applied drugs in critically ill patients is an important issue that needs consideration with the use of all extracorporeal therapies
- Drug removal data derived from in-vitro experiments are informative but not necessarily directly transferable to more complex in vivo conditions
- The clinical relevance of potential drug removal by CytoSorb does not only depend on the impact of the device, but also on drug-specific variables like volume of distribution, protein binding, and half life
- Assessment of clinical relevance of potential drug removal requires consideration of the individual patient condition, impact of concomitantly applied extracorporeal therapies, duration of device exposure, and initiation of drug administration versus steady-state conditions
- CytoSorb drug adsorption kinetics show that most of the adsorption occurs in the first few hours of device exposure. For drugs prone to adsorption, an increased loading dose and/or an additional dose after the first 1–2 hours of treatment should be considered
- Clinical decision-making regarding adjustments in drug dosing should always be made in the broader clinical context, supported by therapeutic drug monitoring when available

1 *CytoSorbents Europe GmbH, Berlin, Germany.*

2 *CytoSorbents Corporation, Monmouth Junction, NJ.*

3 *Adult Intensive Care Unit, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.*

4 *Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland.*

5 *Department of Cardiac Surgery, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.*

6 *Department of Anesthesiology, University Hospital Duesseldorf, Duesseldorf, Germany.*

7 *Department of Pharmacy and Therapeutics, Department of Medicine Renal-Electrolyte Division, University of Pittsburgh, Pittsburgh, PA.*

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For information regarding this article, E-mail: joerg.scheier@cytosorbents.com

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