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REMOVAL CAPABILITY OF CYTOSORB HEMADSORPTION COLUMNS FOR SELECTED PRESCRIPTION DRUGS FREQUENTLY RELATED TO DRUG OVERDOSE

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BACKGROUND AND AIMS

Drug overdose is the leading cause of injury death in the United States, with a 137% increase from 2000 to 2014 [1]. This increase is largely driven by opioid overdose-related deaths. However, prescription non-opioid analgesics, sedatives, antidepressants, and cardiovascular and antipsychotic drugs are further agent classes that are highly relevant with regard to deliberate drug overdose [2].

Currently, the extracorporeal cytokine adsorber CytoSorb (CytoSorbents Europe, Germany) is used mainly for patients with severe infections and sepsis. In the present in vitro study, we analyzed the capacity of CytoSorb columns to remove important representatives of the agent classes mentioned above and the Direct Oral Anticoagulant (DOAC) rivaroxaban from human whole blood.

Table 1: List of used medicinal substances with their respective agent class, intended initial concentration, and therapeutic concentration range

Drug	Agent class	Intended initial concentration(s)	Therapeutic concentration
Amitriptyline	Antidepressant	25 mg/L	0.05 – 0.20 mg/L
Diazepam	Sedative-hypnotic	10 mg/L	0.2 – 2.0 mg/L
Digoxin	Cardiac glycoside	50 µg/L	0.9 – 2.0 µg/L
Ibuprofen	Analgesic	100, 500, 1000 mg/L	15 – 30 mg/L
Paracetamol	Analgesic	400 mg/L	10 – 30 mg/L
Quetiapine	Antipsychotic	7.5 mg/L	0.1 – 0.5 mg/L
Amiodarone	Antiarrhythmic	2.5 mg/L	0.5 – 2.5 mg/L
Rivaroxaban	DOAC	50, 150, 500 µg/L	40 – 400 µg/L

METHODS

The medicinal substances listed in Table1 were added in toxic or therapeutic concentrations to 1 L of human whole blood. Miniaturized CytoSorb columns (scale 1:5; Fig. 1) containing 60 mL of polyvinylpyrrolidone-coated polystyrene-divinylbenzene copolymer beads were applied in an in vitro model system to examine removal rates of the substances from the blood, which was recirculated at a flow rate of 40 mL/min for 300 minutes (Fig. 2).

Briefly, pH was adjusted to a range from 7.35 to 7.45 by administering Tris buffer. Warming of the blood to 37 °C was performed with an infrared blood warmer. Samples were taken after 0, 5, 15, 30, 60, 120, 300 min at the inlet and outlet of the device.

Fig. 1: Miniaturized CytoSorb columns (scale 1:5, V_{ads} = 60 mL) with polyvinyl-pyrrolidone-coated polystyrene-divinylbenzene copolymer adsorbent prior to (left) and during recirculation of human whole blood (right)

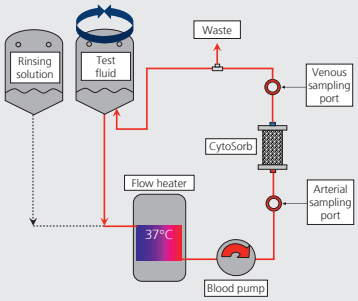

Fig. 2: In vitro recirculation model for investigating the retention of medicinal substances in miniaturized CytoSorb hemadsorption columns (V_B = 1 L, Q_B = 40 mL/min, T = 37 °C)

RESULTS

Considerable removal of amitriptyline, diazepam, digoxin, quetiapine, and rivaroxaban was observed: 87.7 to 96.9% of these administered drugs was rapidly removed from the blood, predominantly within 30 to 60 min of hemoperfusion, resulting in plasma levels near, within or below the respective therapeutic concentration range (Fig. 3).

Paracetamol, ibuprofen, and amiodarone plasma concentrations were only decreased to a limited extent with 13.5, 45.4-59.5, and 50.2% removed mass, respectively. A decrease to and below the respective therapeutic concentration range could not be achieved for these substances.

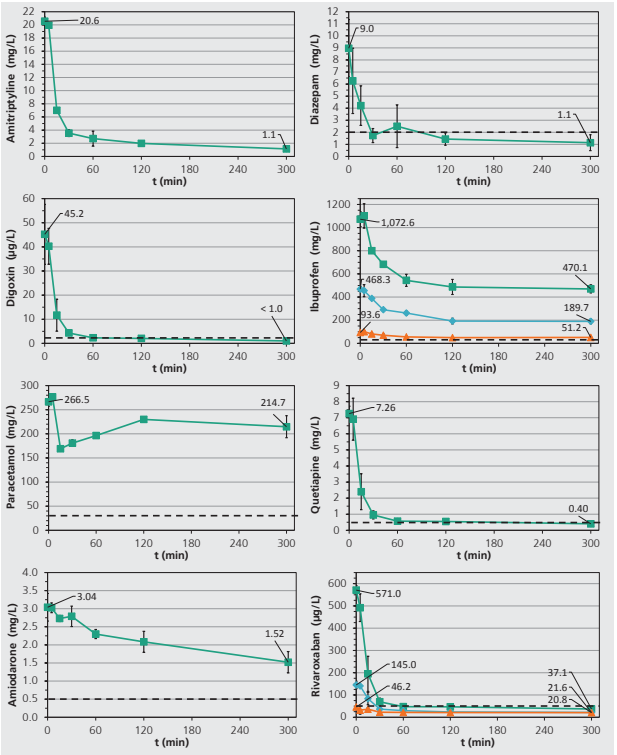

Fig. 3: Inlet plasma concentrations during recirculation of whole blood through CytoSorb columns (Mean ± SD, N = 2). Where applicable, the dashed line represents the therapeutic plasma concentration threshold of the respective drug.

CONCLUSION

Especially for non-dialyzable drugs with a high degree of protein binding, hemoperfusion with CytoSorb columns might be a suitable means to rapidly remove the drugs from the blood in vivo. However, also the volume of distribution (VOD) has to be considered, which is in the order of several 10 to 100 L per kg body weight for some of the used drugs. Because of this extensive distribution into the tissues, the potential therapeutic effect of hemoperfusion with CytoSorb for drug removal in the clinical application requires additional testing in vivo.

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