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Removal of Psychotropic Drugs by Hemoadsorption with the HA380 Cartridge

Taku Furukawa[a] Yugeesh R. Lankadeva[a, b, c] Ian C. Baldwin[d]
Pei Chen Connie Ow[a] Sally Hood[a] Chin Bin Eap[e] Antoine Schneider[f]
Laurent A. Decosterd[g] Rinaldo Bellomo[b, d, h, i, j]

[a]Preclinical Critical Care Unit, Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne, VIC, Australia; [b]Department of Critical Care, Melbourne Medical School, University of Melbourne, Melbourne, VIC, Australia; [c]Department of Anesthesia, Austin Hospital, Melbourne, VIC, Australia; [d]Department of Intensive Care, Austin Hospital, Melbourne, VIC, Australia; [e]Unit of Pharmacogenetics and Clinical Psychopharmacology, Centre for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland; [f]Adult Intensive Care Unit, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [g]Laboratory of Clinical Pharmacology, Department of Laboratory Medicine and Pathology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [h]Department of Intensive Care, Royal Melbourne Hospital, Melbourne, VIC, Australia; [i]Data Analytics Research and Evaluation Centre, Austin Hospital, Melbourne, VIC, Australia; [j]Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, VIC, Australia

Keywords
Valproate · Quetiapine · Escitalopram · Intoxication · Overdose · Blood purification

Abstract

Introduction: Psychotropic drug intoxication may require urgent management. Hemoadsorption (HA) may detoxify blood in such cases, but its effect has not been quantified. ***Methods:*** We studied in vivo removal of valproate, quetiapine, and escitalopram with HA using the Jafron HA380 cartridge in six sheep. We measured the removal ratio (RR) and clearance (CL) of each agent over time. ***Results:*** Mean sorbent-based valproate RR was initially 55.8% (CL: 58.2 mL/min) but declined to negligible levels at 120 min. The mean initial RR for quetiapine was >90% and remained high (72%) at 4 h with CL of 87.2 mL/min at 10 min and 68.7 mL/min at 240 min. The mean RR of escitalopram exceeded 90% at 10 min and decreased to 66.9% at 4 h. The mean CL was 88.0 mL/min at 10 min and 63.2 mL/min at 240 min. ***Conclusion:*** HA with the HA380 cartridge achieves effective removal of valproate, quetiapine, and escitalopram. For valproate, adsorptive performance progressively declined over the 4-h treatment period. In contrast, for quetiapine and escitalopram, the function remained substantial for up to 4 h. Further

Prof. Rinaldo Bellomo passed away during the revision of this manuscript. We respectfully acknowledge his contributions to the study and dedicate this work to his memory.

karger@karger.com
www.karger.com/bpu

Correspondence to:
Taku Furukawa, taku.furukawa@florey.edu.au

Karger

research is required to optimize HA strategies for these drugs and facilitate clinical translation of HA-based blood detoxification.

Introduction

Psychotropic drug intoxication is a common and critical issue in clinical practice that often requires urgent medical management. Traditional management approaches, such as gastrointestinal decontamination, activated charcoal administration, and supportive care, may not always achieve satisfactory outcomes, particularly in severe cases. In such cases, extracorporeal therapies, including hemoadsorption (HA), have been explored as a potential therapeutic option [1–3].

Among the available HA technologies, the Jafron HA series (Jafron Biomedical, Zhuhai, China) represents a newer generation of cartridges designed for HA. These cartridges contain biocompatible macroporous resin beads made from a styrene-divinylbenzene copolymer, which offer a high adsorption capacity [4]. Evidence from case reports and observational studies has suggested the potential efficacy of these cartridges for managing drug intoxication, such as with carbamazepine, digoxin, and metformin [5–8]. However, there remains a lack of data on their efficacy in removing psychotropic drugs, such as valproate, quetiapine, and escitalopram.

These drugs are commonly involved in intoxication scenarios and are associated with severe adverse effects, including central nervous system (CNS) toxicity, hyperammonemic encephalopathy, profound CNS depression, prolonged QTc intervals, and serotonin syndrome [9–11]. They have distinct pharmacokinetic properties that may influence their extracorporeal removal. For example, valproate exhibits high protein binding (87–95%) and a small volume of distribution of 0.1–0.5 L/kg, with a half-life of 6–17 h [9, 12, 13]. Quetiapine is highly lipophilic and protein-bound (~83%) and has a large volume of distribution (6–14 L/kg), with a half-life of ~7 h [14, 15]. Escitalopram is low protein-bound (~56%) and has a large volume of distribution of 12–26 L/kg and a half-life of 27–32 h [16].

We aimed to evaluate the adsorptive performance of the HA380 cartridge for these three commonly prescribed psychotropic drugs using a sheep model of HA. We hypothesized that HA with the HA380 cartridge would result in significant drug removal, but such removal efficiency would progressively decline over time.

Materials and Methods

Animal Preparation

Healthy adult Merino ewes aged 1.5–2.0 years ($n = 6$) with a mean body weight of 39.7 kg (standard deviation [SD] 4.2) were used in this study. The sheep were acclimatized to the laboratory environment for 1 week. They were housed in individual metabolic cages and had unlimited access to 5 L of water and 800 g of oaten chaff daily.

Before the experiment, the sheep underwent aseptic surgery under general anesthesia with isoflurane. The surgery involved cannulating the right carotid artery for arterial blood sampling, the left jugular vein for drug and fluid delivery, and the right jugular vein with a double-lumen catheter (GamCath; Baxter Health Care, Sydney, Australia) for vascular access during HA. The sheep received intramuscular injections of procaine penicillin (900 mg, Ilium; Troy Laboratories, Australia) for antibiotic prophylaxis and flunixin (50 mg, flunixin meglumine injection; Norbrook Laboratories, Australia) for analgesia both pre-surgery and for 2 days post-surgery. The sheep were allowed at least 3 days to recover from the surgery.

Study Design

The experimental protocol is illustrated in Figure 1. General anesthesia was induced with propofol (4 mg/kg) and fentanyl (5 μg/kg) and maintained using a combination of sevoflurane (2–4%), propofol (4 mg/kg/h), and fentanyl (3 μg/kg). An intravenous infusion of compound sodium lactate (1 mL/kg/h) was administered to maintain hydration throughout the study period.

Following induction of general anesthesia, valproate (1.2 g, Epilim EC200; Sanofi-Aventis, Sydney, Australia) was given via an orogastric tube. HA was initiated 75 min later, using a HA380® cartridge and a dedicated system (TR-525® device and JCH-55X2-CHDF-2® circuit; Toray Medical, Tokyo, Japan). HA was conducted as a stand-alone therapy, without additional modalities such as hemodialysis or hemofiltration. The cartridges and circuits were prepared according to the manufacturer's instructions. The circuit was primed with normal saline and both access and return lines were simultaneously connected to the double-lumen catheter. The blood flow rate was initially set at 30 mL/min and incrementally increased to 120 mL/min over 10 min. Anticoagulation was maintained with heparin, administered as a 3,000 IU bolus followed by a continuous

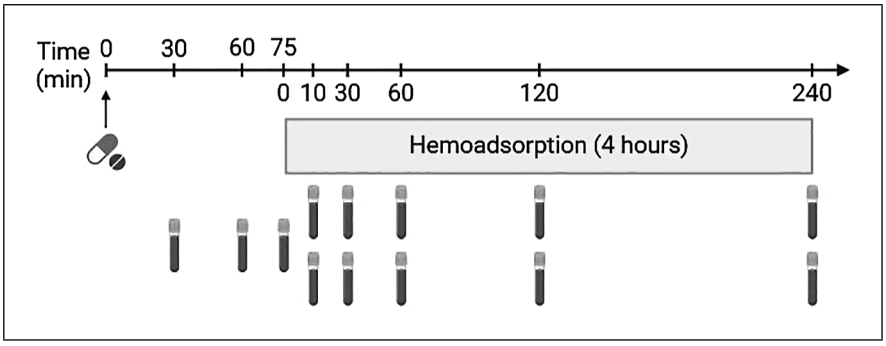

Fig. 1. Description of study protocol. Under general anesthesia, sheep were administered the study drugs via an orogastric tube. Blood samples were collected at 30, 60, and 75 min following drug administration. HA was initiated 75 min after drug administration. During HA, additional blood samples were drawn from two sampling ports positioned before and after the cartridge at 10, 30, 60, 120, and 240 min. HA, hemoadsorption. Figure created with BioRender.

infusion of 2,000 IU/h. The protocol was repeated for a combination of quetiapine (100 mg; Pharmacor, Chatswood, Australia) and escitalopram (30 mg; Sandoz, Sydney, Australia) following a 3-day recovery period.

Collection and Analysis of Blood Samples

Blood samples were collected at 30, 60, and 75 min following drug administration. During HA, additional samples were taken at 10, 30, 60, 120, and 240 min after its initiation. These samples were drawn from two separate sampling ports positioned before and after the cartridge. Blood hemoglobin levels were measured using the ABL Systems 625 analyzer (Copenhagen, Denmark). The Emit® 2000 Valproic Acid Assay (Beckman Coulter, Brea, CA, USA) was used for the measurement of valproate. The plasma concentrations of quetiapine and escitalopram were quantified by high-performance liquid chromatography coupled to tandem mass spectrometry.

Calculation of Sorbent-Based Parameters

The sorbent-based removal ratio (RR), clearance (CL), and mass removal rate (V_{rem}) were calculated at each time point using the following formulas:

$$\text{Removal Ratio (RR, \%)} = \left(1 - C_{post} \,/\, C_{pre}\right) * 100$$

$$\text{Clearance (CL, mg/min)} = Q_p \left(C_{pre} - C_{post}\right)/C_{pre}$$

$$= Q_p * RR$$

$$\text{Mass Removal Rate } \left(V_{rem}, \text{mg/min}\right) = Q_p \left(C_{pre} - C_{post}\right)$$

where C_{pre} and C_{post} represent the drug concentrations measured in the pre- and post-cartridge samples, respectively, and Q_p is the effective plasma flow rate, which was calculated by multiplying the blood flow by the value of 1 minus the hematocrit, with hematocrit approximated as three times the hemoglobin concentration.

Statistical Analysis

Data are expressed as means with standard deviations (SDs). Statistical analyses were conducted using GraphPad Prism® version 10 for Windows (GraphPad Software, Boston, MA, USA). A one-way repeated measures ANOVA with Greenhouse-Geisser correction was applied to evaluate the main effect of "time." Post hoc Dunnett's tests were used for within-animal comparisons between the 10-min time point and subsequent time points. A two-sided p value of ≤0.05 was considered statistically significant.

Results

Impact of HA on Valproate

The changes in plasma concentration, sorbent-based RR, CL, and V_{rem} of valproate are shown in Figure 2. The sorbent-based RR of valproate was initially 55.8% (SD 9.20) at 10 min but declined significantly over time ($p < 0.001$), reaching approximately zero at 120 min. By 240 min, the RR had decreased to −11.2% (SD 18.1) (Fig. 2b). Due to the relatively constant Q_P, changes in CL mirrored those in RR, with a significant decline observed over time ($p < 0.001$, Fig. 2c). CL decreased from 58.2 mL/min (SD 10.2) to nearly zero in 120 min and further decreased to −11.1 mL/min (SD 17.1) by the end of the 4-h procedure. Similarly, V_{rem} exhibited a progressive decrease over time ($p < 0.001$), declining from 1.28 mg/min (SD 0.52) at 10 min to −0.11 mg/min (SD 0.14) at 240 min.

Impact of HA on Quetiapine

As shown in Figure 3b, HA achieved an initial high RR for quetiapine, exceeding 90%. While the RR progressively declined over time ($p < 0.001$), it remained relatively high at the end of the 4-h procedure, at 72.3% (SD 4.4). The CL of quetiapine also demonstrated a

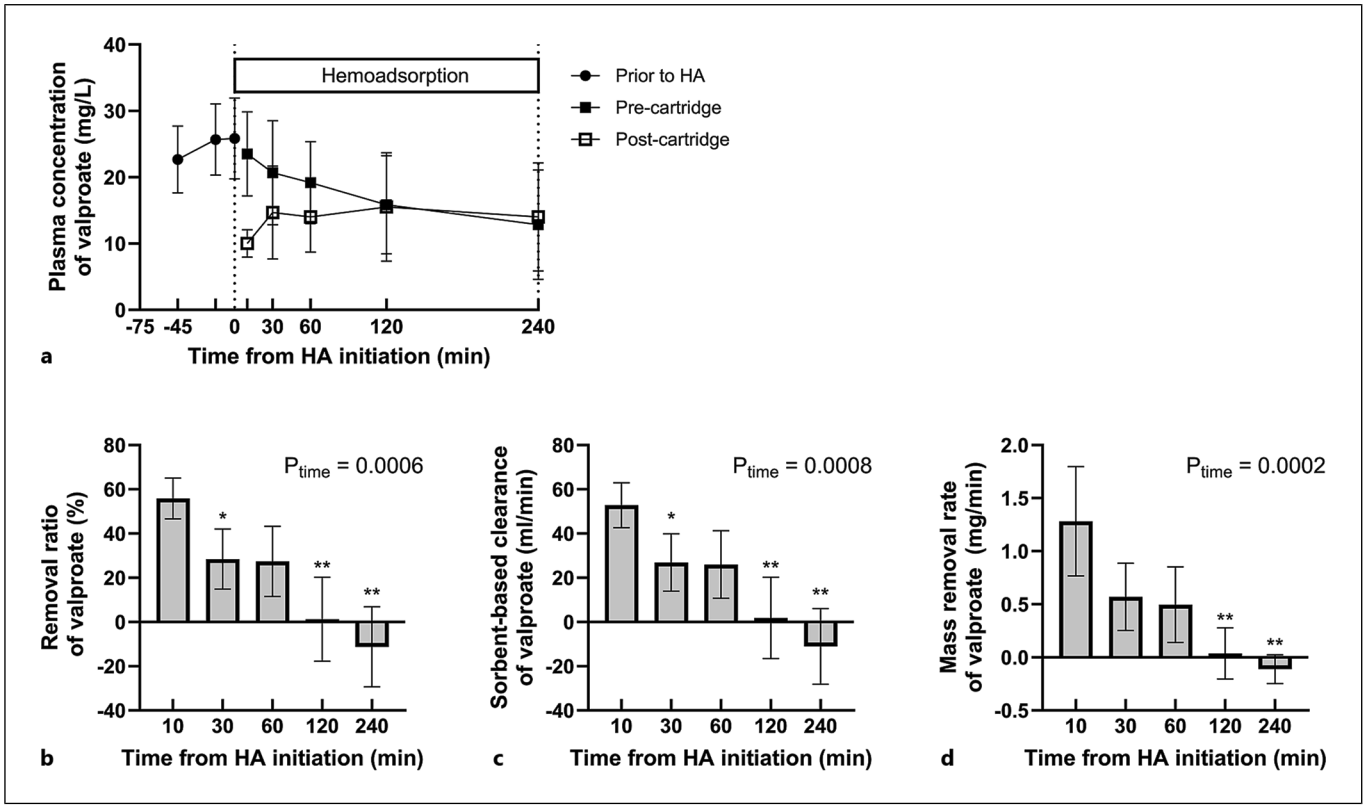

Fig. 2. Impact of HA on valproate. **a** Plasma concentration of valproate. **b** Instantaneous RR. **c** Sorbent-based CL. **d** V_{rem}. Data are shown as mean ± SD, with a sample size of $N = 6$ for all variables. Statistical analysis was performed using one-way repeated measures ANOVA with Greenhouse-Geisser correction for the main effect of "time." *$p < 0.05$, **$p < 0.01$ (post hoc Dunnett's test) compared to the 10-min time point following the initiation of HA. CL, clearance; HA, hemoadsorption; RR, removal ratio; V_{rem}, mass removal rate.

significant decline over time ($p < 0.001$), from 87.2 mL/min (SD 6.2) at 10 min to 68.7 mL/min (SD 7.4) at 240 min (Fig. 3c). Similarly, V_{rem} declined significantly ($p = 0.009$), starting at 10.9 mg/min (SD 6.5) and reaching to 1.98 mg/min (SD 1.14) by the end of the procedure (Fig. 3d).

Impact of HA on Escitalopram

Plasma concentration, sorbent-based RR, CL, and V_{rem} of escitalopram are shown in Figure 4. Like quetiapine, RR of escitalopram exceeded 90%, but decreased significantly over time ($p = 0.003$), reaching 66.9% (SD 14.7, Fig. 4a) at the conclusion of the procedure. The CL of escitalopram also showed a significant decrease ($p = 0.006$), from 88.0 mL/min (SD 7.0) at 10 min to 63.2 mL/min (SD 16.9) at 240 min (Fig. 4c). Although V_{rem} of escitalopram appeared to decrease over time, this trend was not statistically significant. It was 1.46 mg/min (SD 1.9) at 10 min and 0.42 mg/min (SD 0.45) at the end of the procedure (Fig. 4d).

Discussion

Key Findings

In anesthetized sheep with HA using the HA380 cartridge, we demonstrated varying removal efficiencies across different psychotropic drugs. For valproate, moderate initial RR and CL progressively declined to close to zero by 120 min. In contrast, quetiapine and escitalopram exhibited very high RRs and CLs at the initiation of HA, and, although these values decreased over time, RRs and CLs remained substantial, with RRs still 60–70% at the end of the treatment.

Relationship with Previous Studies

Valproate intoxication is relatively common, potentially leading to CNS toxicity. Its elimination through extracorporeal therapies, including HA, hemofiltration, and hemodialysis, has been explored [13]. Although an in vitro study using HA with CytoSorb demonstrated significant valproate removal [17], these results cannot

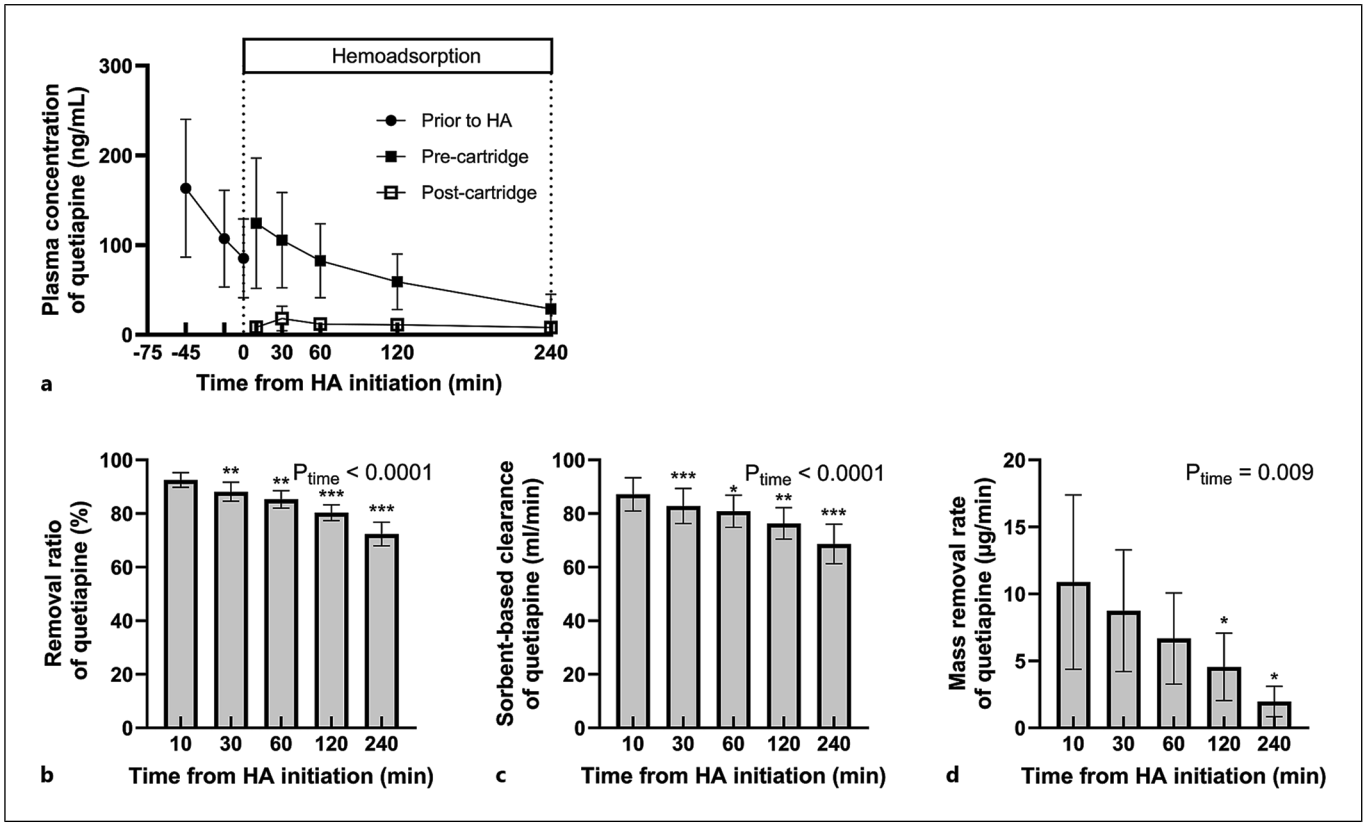

Fig. 3. Impact of HA on quetiapine. **a** Plasma concentration of quetiapine. **b** Instantaneous RR. **c** Sorbent-based CL. **d** V_{rem}. Data are shown as mean ± SD, with a sample size of $N = 6$ for all variables. Statistical analysis was performed using one-way repeated measures ANOVA with Greenhouse-Geisser correction for the main effect of "time." $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ (post hoc Dunnett's test) compared to the 10-min time point following the initiation of HA. CL, clearance; HA, hemoadsorption; RR, removal ratio; V_{rem}, mass removal rate.

be directly extrapolated to in vivo scenarios. This is due to the complexities of pharmacokinetics, including dynamic changes in protein binding during intoxication as well as the in vivo interactions of fibrin deposition, protein layering, and cell covering of the HA beads [18]. A limited number of case reports and case series have described initially moderate to high removal rates with HA, which progressively decline over time – often reaching near-zero levels within a few hours – likely due to increased protein binding (which can exceed 90%) [12] as its concentration declines [19–22]. Our findings are consistent with this pattern. In addition, the saturation of the sorbent cartridge may also contribute to the observed reduction in valproate removal. Importantly, we observed negative RR and CL values at 240 min, suggesting the possibility of desorption (i.e., the release of previously adsorbed drug back into circulation), which has been reported when the cartridges approach their adsorptive capacity [23].

Valproate can also be removed with conventional hemodialysis or hemofiltration [13]. Its low volume of distribution (0.1–0.5 L/kg) suggests, in theory, its suitability for extracorporeal removal. However, its high protein binding (87–95%) under normal conditions [9, 12, 13] limits its removal by conventional modalities of renal replacement therapy (hemodialysis or hemofiltration), which primarily remove unbound drugs. In contrast, HA may be more effective for highly protein-bound drugs due to its ability to adsorb both free and protein-bound fractions. At very high concentrations, however, the protein binding of valproate decreases due to saturation of binding sites, thereby enhancing its removal through dialytic techniques [13]. Further studies are warranted to evaluate the potential of serial or combined extracorporeal therapies for more effective valproate removal.

Quetiapine, an atypical antipsychotic, can cause CNS toxicity, including seizures and QT prolongation [10]. Its

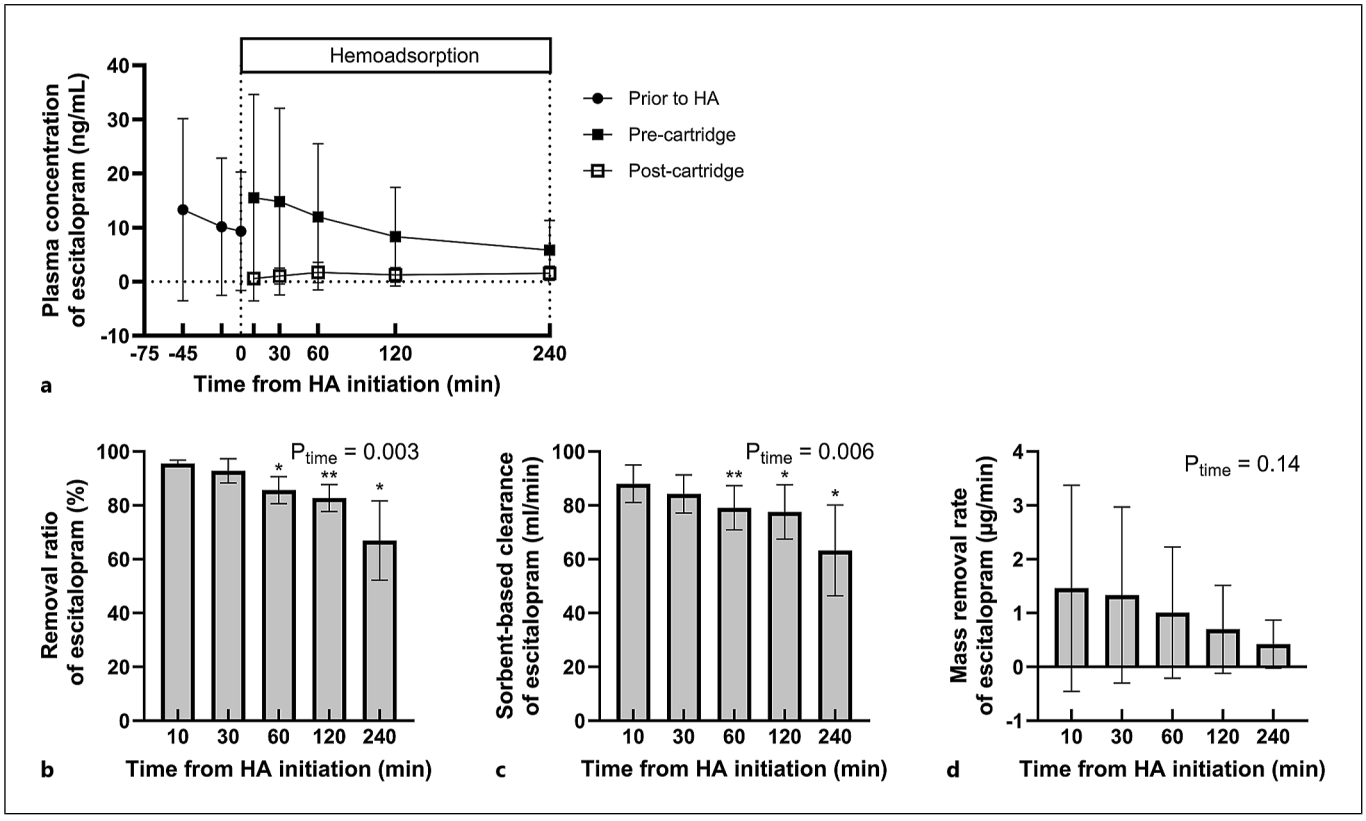

Fig. 4. Impact of HA on escitalopram. **a** Plasma concentration of quetiapine. **b** Instantaneous RR. **c** Sorbent-based CL. **d** V_{rem}. Data are shown as mean ± SD, with a sample size of $N = 6$ for all variables. Statistical analysis was performed using one-way repeated measures ANOVA with Greenhouse-Geisser correction for the main effect of "time." *$p < 0.05$, **$p < 0.01$ (post hoc Dunnett's test) compared to the 10-min time point following the initiation of HA. CL, clearance; HA, hemoadsorption; RR, removal ratio; V_{rem}, mass removal rate.

high lipophilicity (and associated large volume of distribution of 6–14 L/kg) and high protein binding (~83%) [14, 15] limit its removal by dialysis. Thus, HA may be more suitable for quetiapine removal. Only case reports have investigated the effect of HA to enhance quetiapine removal [24–26]. For instance, Reuchsel et al. reported a successful case where HA using CytoSorb, a resin-based sorbent, combined with hemodiafiltration, effectively reduced quetiapine levels, delivered a decrease in concentration across the cartridge, and led to clinical improvement [25]. However, no studies provide an estimate of the percentage removal or CL. Our study is the first to quantify such removal in vivo and corroborates these findings. Importantly, although a large volume of distribution generally reduces the fraction of drug accessible to extracorporeal removal, our results demonstrated sustained removal efficiency over a 4-h treatment period with another sorbent cartridge (the Jafron HA380® cartridge). These findings further support the potential role of HA in managing quetiapine intoxication.

Escitalopram is a selective serotonin reuptake inhibitor and can lead to serotonin toxicity and dose-dependent QT prolongation, both of which pose significant clinical challenges [16]. Although the use of extracorporeal therapies has been reported for the treatment of selective serotonin reuptake inhibitor intoxication [27], no detailed in vivo investigations have been performed to quantify such removal over time when using HA. Escitalopram has a large volume of distribution (12–26 L/kg) and moderate protein binding (~56%), limiting its removal with hemodialysis or hemofiltration [16]. Thus, HA may be a more efficient way of removing the drug. In this regard, our study revealed substantial initial and sustained RRs and CLs with the HA380 cartridge. These findings suggest that HA may be a viable option for managing escitalopram intoxication.

Implications of Study Findings

The variability in drug removal efficiency highlights the importance of optimizing HA protocols to the specific pharmacokinetics and binding properties of each drug to maximize the removal efficiency. Our findings provide valuable insights into the effectiveness of HA using the HA380 cartridge for the removal of commonly prescribed psychotropic drugs. The results suggest that HA may be a practical treatment option for managing intoxication with these drugs. For valproate, however, changes in concentration may significantly increase protein binding to >90% and, thereby, decrease free drug concentration and affect adsorption. In contrast, for quetiapine and escitalopram, the sustained RRs and CLs in the absence of desorption suggest that a single cartridge may suffice for treatment for >4 h before requiring replacement with a new cartridge.

Study Strengths and Limitations

Our study has several strengths. To our knowledge, this is the first study to specifically investigate and quantify the performance of the HA series for the removal of widely used psychotropic drugs. The study was conducted in a large mammalian model, with protocols and doses mirroring clinical practice, thereby enhancing the relevance of our findings.

We acknowledge some limitations. First, the study was conducted in young, healthy sheep. In contrast, patients with drug intoxication often present with various comorbidities, potentially altering drug metabolism and CL. Second, we did not include a sham treatment group to assess endogenous CL of the drugs. However, the observed declines of more than 45% in pre-cartridge plasma concentrations of all three drugs over a 4-h period of HA, despite much longer theoretical half-lives suggest that HA may contribute to their elimination. Nonetheless, pharmacokinetic data, primarily derived from human data, cannot directly be extrapolated without further validation. While inclusion of a control group could have provided additional insights, the highly variable endogenous CL among patients and the common presence of severe renal dysfunction in the setting of severe intoxication make it challenging to replicate all possible clinical scenarios. Moreover, the study did not consider several doses of the drugs and much higher doses might not only lead to earlier saturation of the adsorption capacities but also decrease protein binding and increase CL. Lastly, the blood flow rate of 120 mL/min used in the study was lower than the manufacturer's recommended rate of 200–250 mL/min. However, this flow rate was the maximum achievable in a 40-kg sheep and is comparable to 240 mL/min in an 80-kg patient, maintaining the translational relevance of the study.

Conclusion

In a large mammalian model, we demonstrated the potential of HA using the HA380 cartridge as a viable treatment alternative for psychotropic drug intoxications. The variability in removal between different drugs suggests the need for individualized HA protocols. For valproate, we observed a decline in adsorptive performance, suggesting increased protein binding with lower concentrations. In contrast, with quetiapine and escitalopram, high initial removal with sustained RRs and CLs was observed, and cartridge-based removal remained substantial for up to 4 h. Further research is needed to optimize HA strategies for these drugs and facilitate translation of HA-based detoxification of blood into clinical practice.

Acknowledgments

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Statement of Ethics

We conducted all the experiments following approval from the Animal Ethics Committee of the Florey Institute of Neuroscience and Mental Health, adhering to the guidelines set by the National Health and Medical Research Council of Australia (Approval No. 22-028-FINMH). The study complied with the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines.

Conflict of Interest Statement

This study was funded through an unrestricted research grant provided by Jafron Biomedical, Zhuhai, China. R.B. has received payments from Jafron Biomedical for his role on a Medical Advisory Board and for delivering talks at several meetings. I.C.B., A.S., and R.B. were all members of the journal's Editorial Board at the time of submission.

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Author Contributions

T.F., Y.R.L., I.C.B., P.C.C.O., and R.B. conceptualized and designed the research. T.F., I.C.B., and S.H. conducted the experiments. C.B.E. and L.A.D. oversaw the antibiotic analyses. T.F. performed the data analysis, and T.F., Y.R.L., A.S., L.A.D., and R.B. interpreted the results. T.F. wrote the initial draft of the manuscript. All authors contributed to revising the manuscript and approved the final version.

Data Availability Statement

The data that support the findings of this study are not publicly available due to ethical reasons but are available from the corresponding author on reasonable request.

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