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Vancomycin and Gentamicin Removal with the HA380 Cartridge during Experimental Hemoadsorption

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Keywords
Hemoadsorption · HA380 Jafron cartridge · Gentamicin · Vancomycin · Antibiotics · Sepsis

Abstract
Introduction: Hemoadsorption has emerged as an adjunctive therapy for sepsis, but its impact on antibiotic levels remains poorly defined. We conducted an in vivo experimental study to investigate the removal of vancomycin and gentamicin during hemoadsorption using the HA380 cartridge, a novel styrene-divinylbenzene copolymer cartridge. ***Methods:*** Six surgically prepared sheep were administered 2 g of vancomycin and 400 mg of gentamicin over 30 min, followed by a continuous infusion of vancomycin (20 mg/h). Hemoadsorption was implemented with a styrene-divinylbenzene copolymer HA380 cartridge at a blood flow of 120 mL/min. The removal ratio, sorbent-based clearance, and the mass removal rate were calculated for each time point. ***Results:*** The mean 10-min vancomycin removal ratio exceeded 90% and declined to 68.0% at 30 min; 52.8% at 60 min, and 28.0% by 4 h. Due to constant plasma flow, clearance varied proportionally with the removal ratio. Over 4 hours, the total mass removal was 556 mg (SD 106.3). For gentamicin, the mean 10-min removal ratio was 96.9% and the final ratio at 4 h remained 53.0%, with clearances changing proportionately. The total mass removal of gentamicin was 138 mg (SD 26.6) over 4 h. The sorbent-based clearance of vancomycin was significantly lower than that of gentamicin ($P_{group} < 0.0001$). ***Conclusion:*** The novel HA380 sorbent cartridge appears safe and achieves significant vancomycin and gentamicin removal over a four-hour period. This information can be used by clinicians to guide their prescription and consider the additional dosing of at least an extra 25–35% amount in patients receiving HA380 hemoadsorption therapy during sepsis.

Introduction

Hemoadsorption (HA) has gained attention as an adjunctive therapeutic intervention to mitigate uncontrolled inflammation in intensive care unit patients with sepsis [1]. The clinical benefits of HA are yet to be fully elucidated. However, recent technological advancements in biocompatible materials for sorbents have led to its increased utilization.

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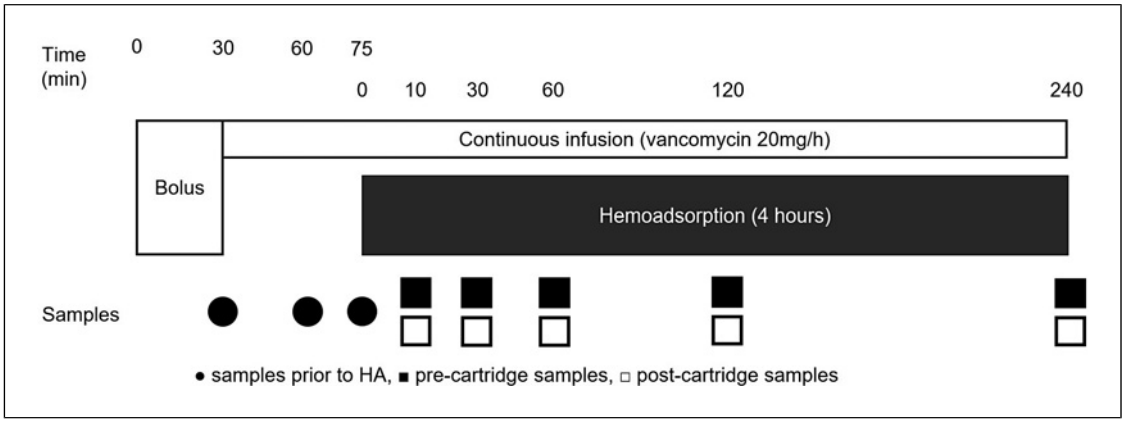

Fig. 1. Schematic description of the study protocol. Vancomycin (2 g) and gentamicin (400 mg) were given intravenously over 30 min followed by a continuous infusion of vancomycin (20 mg/h). HA started 75 min after commencing drug administration. Blood samples were collected 30, 60, and 75 min after the initiation of drug administration. Following the establishment of HA, blood samples were collected 10, 30, 60, 120, and 240 min after the initiation of HA. These samples were obtained from two sampling ports situated before and after the cartridge within the extracorporeal circuit.

The HA330/HA380 cartridges (Jafron Biomedical, Zhuhai, China) are newly developed devices for HA. They contain macroporous resin beads made of a styrene-divinylbenzene copolymer [2]. In a small, randomized controlled trial of 46 patients with sepsis and acute lung injury, HA with HA330 reduced plasma cytokine levels, improved gas exchange, and reduced 28-day mortality [3]. A more recent randomized controlled trial in 30 patients with sepsis showed a reduction in cytokine levels [4]. Despite the removal of inflammatory mediators, the effects of HA with such cartridges on intravenous antibiotics levels remain unclear. Such antibiotic removal may lead to subtherapeutic levels and offset any benefits associated with HA in sepsis.

Given the above concerns, we aimed to test the primary hypothesis that the removal ratio (RR) of vancomycin and gentamicin would be high, and that substantial mass removal would take place. We also aimed to test the secondary hypothesis that such extraction would decrease with time. Finally, we aimed to test the exploratory hypothesis that the RR of vancomycin and gentamicin would differ during such treatment.

Materials and Methods

Animal Preparation

Six healthy female Merino ewes (1.5–2.0 years of age) with a mean body weight of 39.7 kg (standard deviation [SD] 4.2) were used. Before experimentation, sheep were allowed to acclimatize to the laboratory environment for a week. Subsequently, they were housed in individual metabolic cages with free access to 5 L of water and 800 g of oaten chaff food per day.

Preparative surgery for instrumentation was performed under isoflurane general anesthesia. The right carotid artery was cannulated for measurement of arterial pressure, heart rate, and for sampling of arterial blood. The right jugular vein was cannulated with a double-lumen catheter (GamCath®; Baxter Health Care, Sydney, NSW, Australia) for vascular access to perform HA, and the left jugular vein was cannulated for drug and fluid delivery. The sheep received intramuscular injections of antibiotic (procaine penicillin 900 mg; Ilium®; Troy Laboratories, Glendinning, NSW, Australia) and analgesic (flunixin meglumine 50 mg; Norbrook, Australia), just before commencement of surgery and 2 consecutive days postoperatively. Animals were allowed at least 3 days of recovery from the surgical procedure.

Study Protocol

The schematic description of the study protocol is shown in Figure 1. The experiment was conducted under general anesthesia, induced with propofol (4 mg/kg) and fentanyl (5 μg/kg), and maintained with the combination of sevoflurane (2–4%), propofol (4 mg/kg/h), and fentanyl (3 μg/kg).

After induction of anesthesia, sheep received an intravenous infusion of compound sodium lactate (2 mL/kg/h) (Baxter Health Care, Sydney, NSW, Australia) to maintain hydration until the end of the experiment. Vital signs were monitored throughout the experiment. Once animals were stabilized, they received combination therapy comprising 2 g of vancomycin (Alphapharm, Sydney, NSW, Australia) and 400 mg of gentamicin (Pfizer, Sydney, NSW, Australia) intravenously over 30 min followed by a continuous infusion of vancomycin (20 mg/h) until the end of experiment.

HA was implemented with an HA380 cartridge, a dedicated continuous renal replacement therapy machine (TR-525®; Toray Medical, Tokyo, Japan), and corresponding circuit (JCH-55X2-CHDF-2®; Toray Medical, Tokyo, Japan). The cartridges were

prepared according to manufacturer's instruction. Briefly, after injecting 25,000 IU of heparin into the cartridges, they were slowly shaken and rotated and allowed to rest for at least 30 min. They were then pre-rinsed with 500 mL of 5% glucose solution and 2,000 mL of isotonic saline aside from the machine with passive gravity flow over 10–15 min. A third and final 1,000 mL of saline was used to prime by placing the cartridge with circuit into the machine for pump operation and to complete self-test for readiness.

HA began 75 min after commencing drug administration. The blood flow rate was initially set at 30 mL/min and gradually increased within 10 min to maintain a rate of 120 mL/min. Heparin (Heparin Injection®; Pfizer, NSW, Australia) was administered as a bolus of 3000 IU followed by a continuous infusion of 2,000 IU/hr for circuit anticoagulation.

Blood Samples and Analysis

Blood samples were collected 30, 60, and 75 min after the initiation of drug administration. Following the establishment of the extracorporeal circuit, blood samples were collected at 10, 30, 60, 120, and 240 min after the commencement of HA. These samples were obtained from two sampling ports situated before and after the cartridge. Samples were analyzed for blood hemoglobin (ABL Systems 625, Copenhagen, Denmark). The plasma concentrations of vancomycin and gentamicin were analyzed at the Austin Health Pathology laboratory. The Emit® 2000 Vancomycin Assay (Beckman Coulter, Brea, CA, USA) and the Emit® 2000 Gentamicin Assay (Beckman Coulter, Brea, CA, USA) were utilized for the measurement of vancomycin and gentamicin levels, respectively. These assays are based on a homogeneous enzyme immunoassay method.

Parameters and Calculations

The RR (percentage of drug removal by the sorbent), sorbent-based clearance (CL; drug CL by the sorbent), and mass removal rate (v_{rem}; rate of drug removal by the sorbent) were calculated for each time point as follows:

$$RR\ (\%) = (1 - C_{pre}/C_{post}) \times 100$$

$$CL\ (mg/min) = Q_p\ (C_{pre} - C_{post})/C_{pre} = Q_p \times RR$$

$$v_{rem}\ (mg/min) = Q_p\ (C_{pre} - C_{post})$$

where C_{pre} is the concentration of drug in the pre-cartridge sample, C_{post} is the concentration in the post-cartridge sample, and Q_p is the effective plasma flow assessed as the product of blood flow multiplied by the value of 1 minus hematocrit which was estimated by multiplying the hemoglobin by a factor of three. The mass removal by the sorbent (M_{rem}) between time points was calculated as the area under the curve of the v_{rem} using the logarithmic trapezoidal rule. Hourly mass removal (hourly M_{rem}), representing the average mass removal per hour during each period, was calculated as M_{rem} divided by the duration of the period. Additionally, cumulative mass removal was also calculated.

Statistical Analysis

Data are presented as means and SDs. Analysis was performed using GraphPad Prism® for Windows, version 9 (GraphPad Software). First, one-way repeated measures ANOVA was conducted with a Greenhouse-Geisser correction applied to the main effect of "time." Within-animal pairwise comparisons between each time point and the 10-min time point were performed using post hoc Dunnett's test. For between-group comparison, two-way ANOVA was applied with Sidak's multiple comparison test. A p value ≤0.05 was considered statistically significant.

Results

Safety of HA380 HA on Blood Pressure and Heart Rate

During the experiment, mean arterial pressure and heart rate remained stable (Fig. 2) and there were no safety concerns.

Removal of Vancomycin during HA

Plasma vancomycin and gentamicin concentrations, along with the calculated RRs, CLs, and v_{rem} at each time point, are shown in Figures 3 and 4. The mean RR of vancomycin decreased over time during HA. It exceeded 90% at 10 min but declined to 68.0% (SD 7.1) at 30 min and 52.8% (SD 9.9) at 60 min. The rate of decrease gradually slowed down, reaching an RR of 28.0% (SD 9.1) by 4 h (Fig. 3b).

Due to the relatively constant effective plasma flow, the CL varied proportionally with the RR from a mean of 83.4 mL/min (SD 4.3) at 10 min to 48.8 mL/min (SD 8.7) at 1 h and 25.6 mL/min (SD 7.0) at the end of the experiment (Fig. 3c). V_{rem} of vancomycin also exhibited an exponential decay during HA (Fig. 3). As shown in Table 1, the hourly M_{rem} of vancomycin progressively decreased from 410.7 mg/h (SD 65.2) between 10 and 30 min to 77.6 mg/h (SD 19.9) during the last 2 h for a cumulative mass removal of 556 mg (SD 106.3), accounting for 26.7% (SD 5.1) of the total dose, with 46.7% (SD 3.8) of the total occurring in the first 60 min.

Removal of Gentamicin during HA

Like vancomycin, during HA there was a progressive decline in the RR and CL of gentamicin; however, the decrease was slower and lesser. Thus, the mean RR at 10 min was 96.9% (SD 0.6) and the final ratio at 4 h remained above 50% (53.0% [SD 9.2]) (Fig. 4b). CL for gentamicin was 89.7 mL/min (SD 4.3) at 10 min and 49.1 mL/min (SD 7.2) at 4 h (Fig. 4c).

The v_{rem} of gentamicin decreased from 1.97 mg/min (SD 0.29) at 10 min to 0.15 mg/min (SD 0.04) at the end of the experiment (Fig. 4d). The hourly M_{rem} decreased from 100.9 mg/h (SD 15.1) between 10 and 30 min and 16.2 mg/h (SD 5.1) in the period between 120 and 240 min. The cumulative mass removal of gentamicin over the 4-h period was 138 mg (SD 26.6), accounting for 34.6% (SD 6.7) of the total dose of 400 mg with 49.0% occurring in the first 60 min (Table 2).

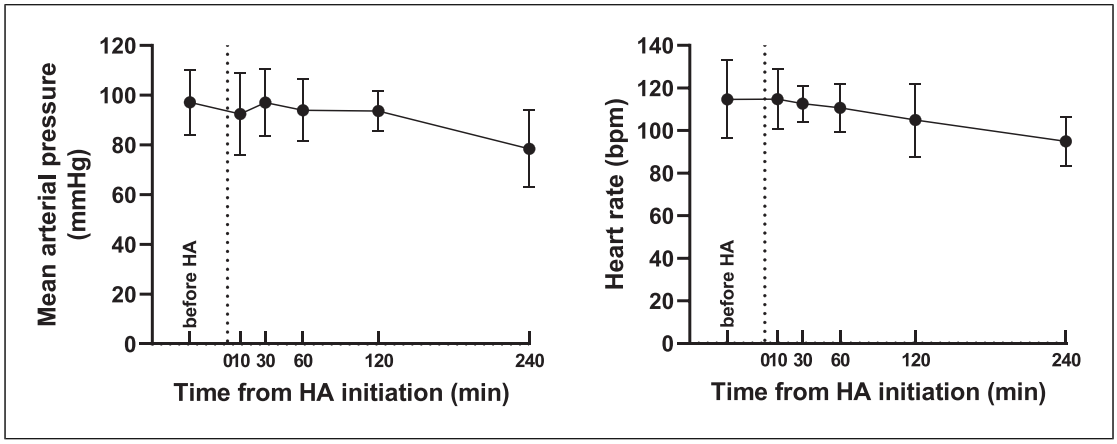

Fig. 2. Mean arterial pressure and heart rate during the experiment (n = 5). The average values during the preceding 3 min at each time point are presented. The values prior to HA ("before HP") are represented as the average values of the last 3 min before the initiation of HA. Data are presented as mean and SD. HA, hemoadsorption; SD, standard deviation.

Comparison between Removal of Vancomycin and That of Gentamicin

The overall CL of vancomycin was significantly less than that of gentamicin ($P_{group} < 0.0001$) with significant differences at each individual sampling time, except for the 10-min time point (Fig. 5).

Discussion

Key Findings

In anesthetized healthy sheep undergoing HA with a novel HA380 styrene-divinylbenzene copolymer cartridge, blood pressure and heart rate remained stable during treatment. In these animals, vancomycin and gentamicin removal and CL were prominent at the very start of treatment but progressively and significantly decreased over the 4 h of treatment. Moreover, total mass removals of both drugs during HA with the HA380 cartridge appeared clinically relevant and accounted for 25–35% of the total administered intravenous dose. Finally, sorbent-based CL of vancomycin was significantly lower than that of gentamicin.

Relationship to Previous Studies

The progressive decline in sorbent-based CL of vancomycin and gentamicin during HA in our study is consistent with previous ex vivo and human studies. In a study using an experimental circulation model with isotonic saline, a mini-cartridge, and high concentrations of vancomycin to determine the maximal total amount of removal in grams, the concentration of vancomycin showed a rapid exponential decay. Maximum removal occurred in the early stages of HA and reached close to zero by the end of the 5-h experiment, indicating full saturation of the sorbent after exposure to 10 g of the drug [5]. However, information obtained in a saline-based model does not reliably reflect events when a cartridge is exposed to blood because of coating of the sorbent with cells and fibrin. Moreover, the large amount of vancomycin applied in a closed circuit is not clinically relevant.

A prospective observational study in seven patients with septic shock demonstrated significant adsorption of vancomycin by a resin adsorber cartridge, with a linear decrease during HA with the CytoSorb® cartridge [6]. The authors proposed an additional 500 mg dose of vancomycin over 2 h at the initiation of HA to compensate for removal by the procedure. Similar needs for adjustment were reported in another observational clinical study [7]. Our findings suggest that similar dose adjustment would be necessary with the HA380 cartridge. We could not identify any previous studies of gentamicin extraction during HA.

We identified a significant difference in adsorptive performance for vancomycin and gentamicin. Variation in sorbent-based CL between different drugs has been observed in previous studies using different cartridges [8, 9]. The HA380 cartridges are designed to target the removal of hydrophobic or protein-bound substances within a wide molecular weight range [10]. Vancomycin has a molecular weight of 1,449 Da, and gentamicin has a molecular weight of 477 Da [11, 12]. As their molecular weights are both well below the target range of the

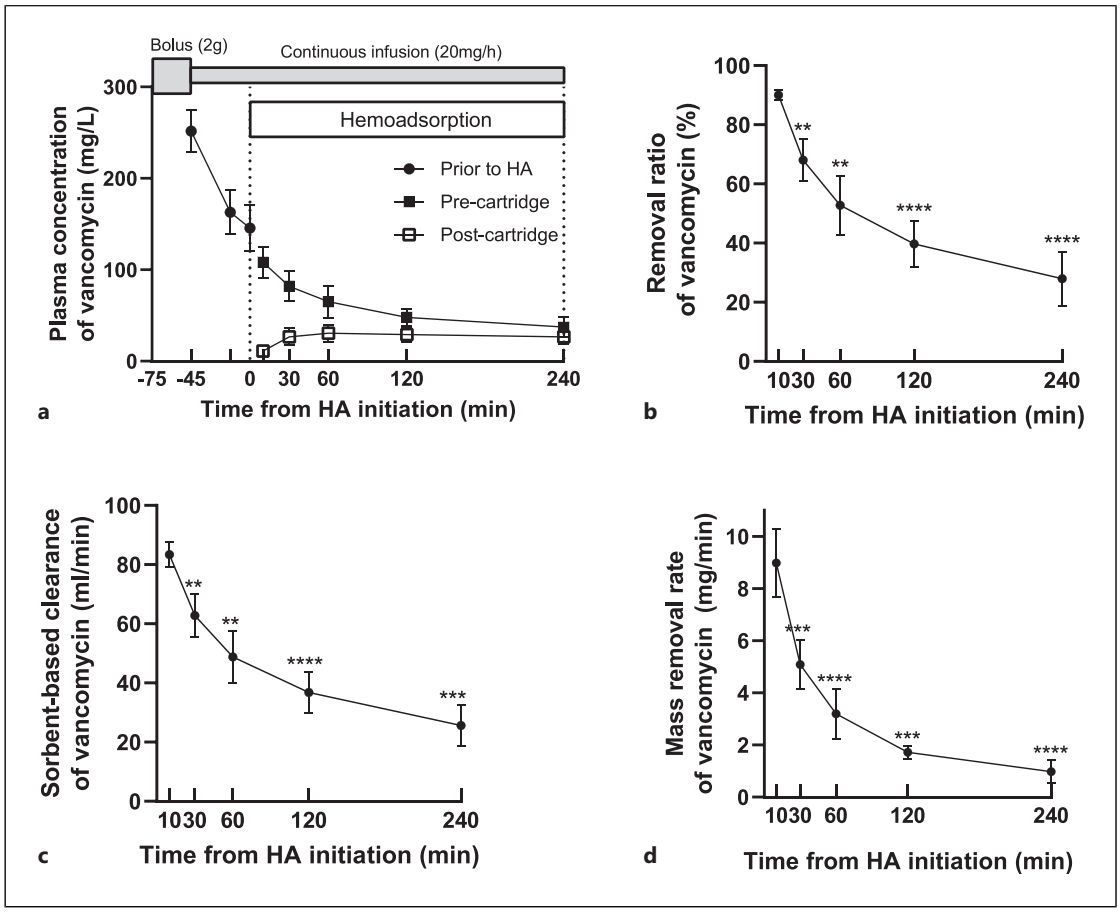

Fig. 3. Effects of HA on vancomycin. **a** Plasma concentration of vancomycin. **b** The RR. **c** The sorbent-based CL. **d** The v_{rem}. Data are presented as mean and SD. There are 6 observations for all variables. Data were subjected to one-way repeated measures ANOVA with a Greenhouse-Geisser correction applied to the main effect of "time." $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$ (post hoc Dunnett's test) for comparison with the 10-min after initiation of HA. HA, hemoadsorption.

cartridge, they should be removed in a similar way. However, 50–70% of vancomycin in plasma is protein bound [13], compared with less than 30% for gentamicin [11]. Our observations show that substances with appreciable protein can be significantly removed by HA380, but they also suggest that the impact of protein binding on drug removal may not be fully overcome even with novel sorbents.

The total mass removal of vancomycin and gentamicin we report must be viewed within the context of the very high doses delivered to our experimental animals. This was done to ensure that, even in the presence of very high adsorption and renal excretion, sufficient plasma levels would be present to study adsorptive removal and CL. The maximal ex vivo adsorption capacity of the HA380 cartridge for vancomycin is as high as 24.4 g [5]. This suggests that the decrease in v_{rem} over time was not limited by the saturation capacity of the sorbent, but rather by other factors. This likely applies to gentamicin as well.

Implications of Study Findings

Our study suggests that HA with the HA380 cartridge is hemodynamically tolerated. It highlights the impact of the HA380 cartridge on antibiotic removal in critically ill patients. Moreover, it provides novel data suggesting that the findings from one agent cannot be extrapolated to another. Finally, although mass removal is obviously influenced by circulating drug levels, we can estimate that, at an average RR of 50%, in a patient with levels of 25 mg/L, and a plasma flow of 160 mL/min through the sorbent cartridge (approximately 1 L every 6 min), 500 mg of vancomycin would be removed in 4 h. Such concepts should also apply to gentamicin.

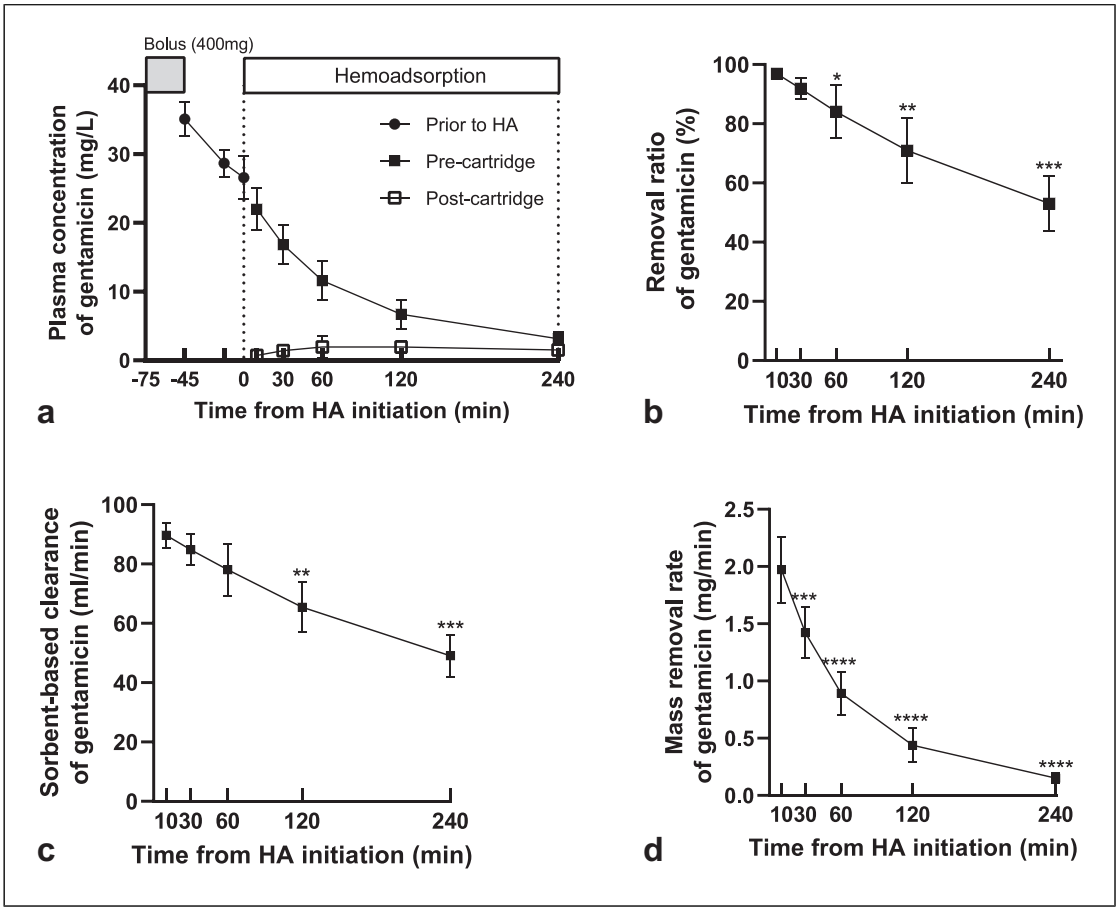

Fig. 4. Effects of HA on gentamicin. **a** Plasma concentration of gentamicin. **b** The instantaneous RR. **c** The sorbent-based CL. **d** The v_{rem}. Data are represented as mean and SD. $N = 6$ for all variables. Data were subjected to one-way repeated measures ANOVA with a Greenhouse-Geisser correction applied to the main effect of "time." *p <0.05, **p <0.01, ***p <0.001, ****p <0.0001 (post hoc Dunnett's test) for comparison with the 10-min after initiation of HA. HA, hemoadsorption.

Table 1. Mass removal of vancomycin during HA

	Vancomycin (total dose: 2,085 mg)		
	Mass removal, mg	Cumulative mass removal, mg	Hourly mass removal, mg/h
Period (time after HA initiation)			
10–30 min	136.9 (21.7)	–	410.7 (65.2)
30–60 min	121.7 (28.4)	258.6 (49.6)	243.5 (56.8)
60–120 min	142.3 (31.9)	400.9 (79.4)	142.3 (31.9)
120–240 min	155.1 (39.9)	556.0 (106.3)	77.6 (19.9)

Data are expressed as mean (SD). HA, hemoadsorption.

Study Strengths and Limitations

To the best of our knowledge, this is the first in vivo experimental study to investigate the adsorptive performance of the HA380 cartridge for two commonly used intravenous antibiotic drugs. The HA380 cartridge is in clinical use and was studied in a large mammalian model, which increases clinical relevance. Our observations have clinical implications and highlight the fact that different

Table 2. Mass removal of gentamicin during HA

	Gentamicin (total dose: 400 mg)		
	Mass removal, mg	Cumulative mass removal, mg	Hourly mass removal, mg/h
Period (time after HA initiation)			
10–30 min	33.6 (4.6)	–	100.9 (15.1)
30–60 min	34.1 (5.6)	67.7 (10.1)	68.2 (12.2)
60–120 min	38.2 (8.7)	106.0 (18.2)	38.2 (9.5)
120–240 min	32.3 (9.3)	138.3 (26.6)	16.2 (5.1)

Data are expressed as mean (SD). HA, hemoadsorption.

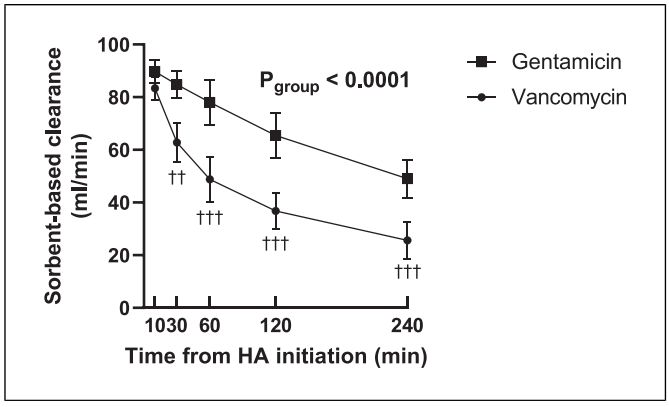

Fig. 5. Sorbent-based CL of vancomycin and gentamicin (n = 6). Data are represented as mean and SD. Data were subjected to two-way ANOVA. $^{††}p$ <0.01, $^{†††}p$ <0.001 (Sidak's test) for comparison between vancomycin and gentamicin for each time point. HA, hemoadsorption.

antibiotics have different interactions with the sorbent and need to be studied separately.

We acknowledge some limitations. First, the experiment was conducted in healthy sheep. Critically ill patients with sepsis typically have acute kidney injury, which adds further complexity to drug CL. Second, the blood flow rate of 120 mL/min was lower than the recommendation of the manufacture (200–250 mL/h). However, this flow rate was the highest achievable in a 40 kg sheep and would be equivalent to 240 mL/h in an 80 kg human. Third, our circuit was anticoagulated with heparin. Citrate anticoagulation may affect adsorption differently. However, heparin-based anticoagulation of HA circuits remains common. Fourth, the observed differences in sorbent-based CL between vancomycin and gentamicin might be influenced by variations in the dose and administration method. However, since sorbent-based CL is calculated as the product of effective plasma flow and the RR, it is primarily determined by the interaction of the cartridge with each specific drug. Finally, we did not include a sham treatment group in our study to assess endogenous CL. However, the endogenous CL of these drugs in the clinical intensive care unit situation varies tremendously from supranormal in young trauma patients, all the way to absent in septic shock patients with anuric kidney injury. Thus, it is not logistically possible to simulate all these situations in large animal studies of HA.

Conclusion

Our study showed that HA with the HA380 cartridge is well tolerated hemodynamically and that a very strong initial adsorption was followed by temporal decline in the RR and sorbent-based CL of vancomycin and gentamicin. This suggests the need for dose adjustment/top-up by 25–35% of these antibiotics to maintain therapeutic levels. Furthermore, the variation in sorbent-based CL for these two drugs emphasizes the importance of considering the adsorptive performance of the cartridge for individual drugs. Further research is warranted to investigate the adsorptive performance of this novel cartridge for different drugs.

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Statement of Ethics

Procedures were conducted after approval by the Animal Ethics Committee of the Florey Institute of Neuroscience and Mental Health under the guidelines of the National Health and Medical Research Council of Australia, approval number 22-028-FINMH. The study conformed with the Animal Research: Reporting of In Vivo Experiments (ARRIVE) criteria.

Conflict of Interest Statement

This study was supported by an unrestricted research grant by Jafron Biomedical, Zhuhai, China. Rinaldo Bellomo has received payment from Jafron Biomedical as a member of a Medical Advisory Board and consultancy fees as speaker at several meetings.

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Author Contributions

T.F., Y.R.L., I.C.B., P.C.C.O., C.N.M., and R.B. conceived and designed the research; T.F., I.B., and S.H. performed the experiments. T.F. analyzed data; T.F., Y.R.L., and R.B. interpreted the data. T.F. and R.B. drafted the manuscript. All authors edited and revised the manuscript and approved the final version.

Data Availability Statement

Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

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