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Vancomycin Adsorption during in vitro Model of Hemoperfusion with Mini-Module of HA380 Cartridge

Anna Lorenzin[a, b] Massimo de Cal[a, b] Matteo Marcello[b] David Sorbo[a, b]
Sabrina Copelli[c] Claudio Ronco[a, b] Silvia de Rosa[b] Monica Zanella[a, b]

[a]Department of Nephrology, Dialysis and Transplantation, St. Bortolo Hospital, Vicenza, Italy; [b]International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy; [c]Department of Science and High Technology, Università degli Studi dell'Insubria, Varese, Italy

Keywords
Hemoadsorption · Adsorption · Hemoperfusion · Vancomycin · Sepsis

Abstract
Introduction: Sepsis is a frequent complication in critically ill patients. Patients may require control of the source of infection, removal of pathogens and damaged cells, and organ support. Often, these targets can be achieved through the utilization of extracorporeal therapies including hemoperfusion for the adsorption of cytokines and other circulating mediators. On extracorporeal organ support, patients are generally treated with antibiotic therapy, and vancomycin is one of the most commonly used antibiotics. Because of the aspecific nature of adsorption, antibiotics can be removed from the circulation, leading to altered plasma levels and requiring prescription adjustment. The aim was to define the amount of vancomycin adsorbed by a sorbent cartridge (HA380, Jafron, China) during hemoperfusion and to establish possible strategies to maintain an effective plasma level in critically ill patients undergoing extracorporeal therapies. ***Methods:*** In vitro experiments with incremental concentrations of vancomycin in the test solution (500 and 1,000 mL) were carried out in a recirculation circuit until sorbent saturation was observed. A maximum of 10 g of vancomycin were injected and mini-modules containing 25 g of dry resin were utilized. ***Results:*** In different experiments with various concentration of vancomycin, a maximum amount of 244 mg/g of sorbent was adsorbed reaching saturation between 60 and 80 min from the beginning of the experiments. The kinetics of adsorption appears to be governed by a Langmuir-like isotherm with maximal removal speed in the early minutes and a plateau after 60 min. ***Discussion/Conclusion:*** HA380 adsorbs significant amounts of vancomycin. Adjusting the achieved results with the experimental mini-module to a full-scale cartridge, a total of 25 g of antibiotic can be removed. This might have affected outcome results in clinical trials. This suggests prescribing administration to critically ill patients requiring hemoperfusion, immediately after or in the inter-session time window. In case of administration during hemoperfusion, adequate adjustment and plasma level monitoring is strongly recommended.

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

Correspondence to:
Anna Lorenzin, lorenzin.anna@gmail.com

Introduction

Sepsis is one of the most frequent causes of admission to the intensive care unit (ICU) and it carries a high risk of mortality [1, 2]. About one third of patients with sepsis develop AKI [3] or other organ dysfunctions that contribute to a worse prognosis. Sepsis-associated AKI (s-AKI) is the result of a dysregulated host immune response to infection [4], with the production of chemical mediators and cytokines that cause hemodynamic alterations, endothelial damage, cell apoptosis, and an imbalance between inflammation and immune-paralysis.

In recent years, there has been a growing interest in extracorporeal techniques that could remove from the bloodstream molecules produced or released by pathogens and damaged cells during sepsis. Among different extracorporeal techniques, hemoperfusion with sorbent cartridges has recently gained particular attention [4]. The increased hemocompatibility of new sorbent materials and the excellent flow-dynamic design of modern adsorption units allow us to put the patient's blood in direct contact with the sorbent in an extracorporeal blood purification technique defined as "hemoperfusion" (HP).

In such a technique, adsorption operates as a mass removal mechanism based on chemical and physical bonds between the polymer-based sorbent contained in the cartridge and various circulating molecules (i.e., molecules in the fluid phase represented by blood). These interactions depend on the physical-chemical properties of the molecule as well as on the nature and characteristics of the surface (porosity, diameter of the pores, ions, and counter ions on the surface) [5, 6]. Sorbent cartridges can be used alone (isolated hemoperfusion) or in series with a hemodialyzer. Hemoperfusion and hemodialysis (or continuous renal replacement therapy) can also be applied in sequence in the case of sepsis to promote cytokine removal first and, subsequently, kidney support (sequential extracorporeal therapy) [7, 8].

Among other products, significant experience has been matured with the HA 330/380 adsorbent cartridges (Jafron Medical, China), used in HP or HP + continuous renal replacement therapy or HP + HD in critically ill patients with sepsis and acute respiratory failure, with promising results in terms of biological, clinical, and physiological improvements [9, 10]. The application of these methods has been further extended to other acute (hepatitis and pancreatitis [11, 12], intoxications [13–15]) and chronic conditions (control of itching in chronic hemodialysis patients [16]). Biological studies [17] have shown an excellent biocompatibility of these materials without side effects or signs of cytotoxicity. Clinical experience, although significant and meaningful, requires further studies on several aspects that have not been completely elucidated yet, such as dose and duration of the sessions, optimal blood flow, and measures of adequate prescription and delivery. The first aspect requires a careful analysis of the isotherm curves for specific molecules in order to elucidate the kinetics of removal from blood, efficiency of the sorbent unit, and overall amount of solute leading to unit saturation.

Among the unanswered questions, we can underline the potential adsorption and removal from the blood of beneficial substances and drugs whose levels in the blood are essential for an adequate therapeutic response, as in the case of antibiotics. The adsorption of these molecules could determine, in addition to therapeutic failure, an increased risk of selecting drug-resistant bacterial strains.

In particular, the problem of resistance to vancomycin is increasingly emerging in ICUs, as evidenced by the increase in cases of infection with gram-positive bacteria resistant to this drug, in particular *enterococci*. Previous studies have also shown that there is a wide inter-individual variability in the achievement of the pharmacokinetic and pharmacodynamic targets of vancomycin [18]. For these considerations, it would be quintessential to define the adsorption capacity of sorbent cartridges for a molecule such as vancomycin.

The Jafron HA330/HA380 cartridge series has been designed for use in clinical conditions characterized by elevated cytokine levels such as sepsis and other cytokine release syndromes. A recent in vitro study by our group aimed at evaluating vancomycin-cartridge interactions independently of other factors affecting pharmacokinetics, showing that the administration of repeated doses of vancomycin results in cumulative adsorption with a linear relationship between the amount introduced and the amount adsorbed [19].

The aim of the present study was to determine the amount of vancomycin per gram of the neutral microporous resin utilized in the Jafron HA 330/380 units required to completely saturate all sites available for adsorption. For this purpose, an experimental in vitro circuit with sorbent mini-modules was utilized in a laboratory setup under accurately defined experimental conditions (temperature, amount of resin, amount of vancomycin, time-defined drawings, and measurements). The final scope was to offer clinicians the important information about vancomycin kinetics during hemoperfusion and suggest the most effective prescription of such antibiotic therapy during sorbent-based blood purification techniques.

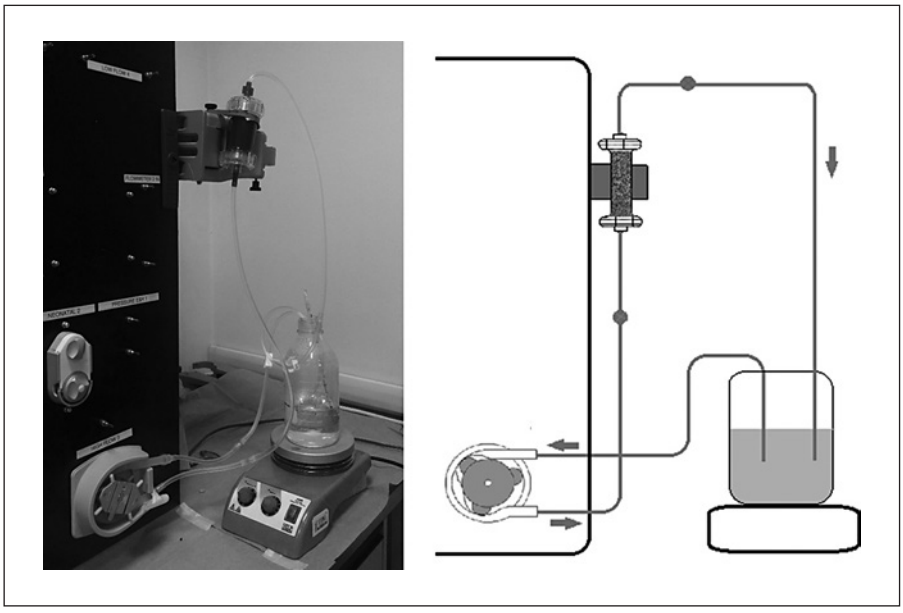

Fig. 1. In vitro experimental setup. A customized extracorporeal circuit with HA380 mini-module is applied to Galileo testing platform. The reservoir is positioned on a magnetic hotplate stirrer.

Materials and Methods

The Sorbent Studied

Experiments were conducted in vitro to determine the adsorption capacity for vancomycin of Jafron neutro-macroporous resin. Sorbent beads are made of styrene-divinylbenzene copolymer with an average diameter of 0.80 mm, ranging from 0.60 to 1.0 mm. The pore size diameters of the resin are distributed in a wide range of dimensions, allowing adsorption of solutes between 500 and 60,000 Da. Solute removal from the blood is achieved through different interaction forces (ionic bonds, van der Waals forces, hydrophobic bonds). Due to the specific sterical configuration and elevated surface area, the resin can adsorb a significant amount of variety of molecules, among them antibiotics such as vancomycin, as previously demonstrated. The study was designed to establish the maximum capacity of adsorption of the antibiotic per gram of resin.

The Experimental Circuit

In vitro circulation was performed using a dedicated testing platform developed in our institute (Galileo), equipped with pressure sensors and peristaltic pumps. A scaled closed-loop HP circuit was created with the setup described in Figure 1. In order to evaluate the resin saturation point, a customized cartridge was built by assembling a sorbent mini-module (25% of the regular size HA380 cartridge) containing 75 g of wet resin (approximately 25 g of dry resin).

The device was primed according to the instructions for use. The peristaltic pump was set at 250 mL/min and the circuit was operated in recirculation mode using a fixed volume of saline solution (500 mL) in which vancomycin was added. During the experiments, the solution was warmed and maintained at 37°C and mixed with a magnetic hotplate stirrer. After previous experiments using whole blood, we decided to utilize in these tests a saline solution to avoid interferences due to plasma proteins and other blood components. While these may reduce the adsorption capacity in vivo, they may render the observation inaccurate and highly variable. The purpose of the current study is to analyze maximal adsorption capacity in ideal conditions, recognizing that in vivo results may report lower values depending on the operational conditions and blood composition.

Experimental Setup

Several experiments were conducted to ensure that adsorption material saturation was reached. For this purpose, in every experiment a batch of 500 mL of saline solution was spiked with progressively increasing amounts of vancomycin.

We pursued two different approaches: In Protocol a, repeated boluses of 100 mg of vancomycin were administered in the saline solution reservoir. Samples were collected after 5 min (vancomycin equilibration in static conditions) and after 10 and 20 min of circulation to determine the progressive adsorption. A new bolus was injected when a concentration reduction higher than 90% was reached in the fluid batch. When the percent reduction was lower than 90%, the circulation was continued and the percentual adsorption was assessed again after another 10-min time interval. In Protocol b, we performed two experiments with two batches of saline spiked from the beginning with an extremely high quantity of vancomycin (5,000 mg in 500 mL and 10,000 mg in 1,000 mL) and we tested adsorption up to 300 min. Samples were collected every 20 min.

Vancomycin Measurement and Samples Handling

Vancomycin is a widely used antibiotic, especially in critically ill patients admitted to intensive care units (Fig. 2). Before spiking the test solution with the defined dose, vancomycin was reconstituted according to the manufacturer's recommendations. Samples were taken in triplicate to ensure the measured concentration in the initial batch was consistent with the amount injected (Fig. 3). Collected samples (3 mL) were analyzed. Vancomycin concentra-

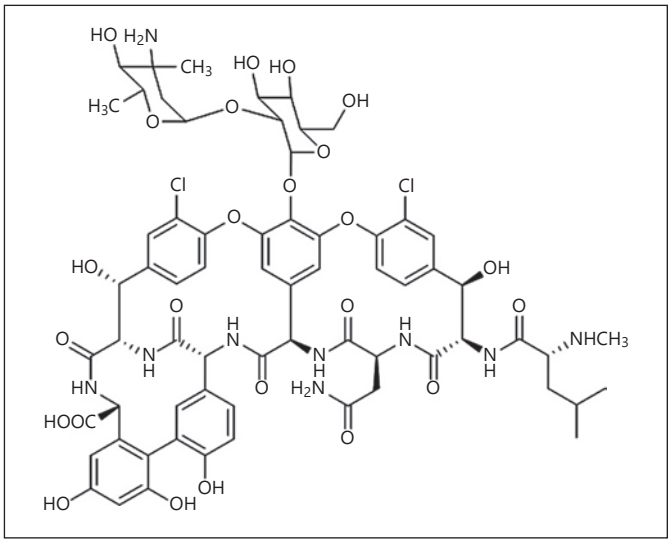

Fig. 2. Vancomycin chemical formula. Vancomycin is a bactericidal agent that binds to the bacterial cell wall causing blockage of glycopeptide polymerization. The bactericidal action results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis. The formula is $C_{66}H_{75}Cl_2N_9O_{24}$ and the molecular weight is 1,449.2 g/mol (1 g/mol = 1 Da) with solubility in water: greater than 100 mg/mL. Isoelectric point is at pH 5 with dissociation constants: pka1 = 2.6; pKa2 = 7.2; pKa3 = 8.6; pKa4 = 9.6; pKa5 = 10.5; pKa6 = 11.7. When reconstituted as directed in 0.9% sodium chloride injection or 5% dextrose injection, solutions prepared from ADD-Vantage vials of the drug are stable for 24 h at room temperature. Vancomycin is approximately 55% serum protein bound. The mean elimination half-life of vancomycin from plasma is 4–6 h in subjects with normal renal function. In anephric patients, the average half-life of elimination is 7.5 days. In adults with normal renal function who received multiple 1 g doses of vancomycin (15 mg/kg) given by IV infusion over 1 h, mean plasma concentrations immediately after completion of the infusion are approximately 63 μg/mL and mean plasma concentrations 2 and 11 h later are approximately 23 or 8 μg/mL, respectively. When multiple 500-mg doses are given by IV infusion over 30 min, mean plasma concentrations are about 49 μg/mL immediately following the infusion and about 10 μg/mL 6 h after infusion.

tions were measured using the QMS assay (Thermo Fisher Scientific, Waltham, MA, USA) using the ILab 650 platform (Instrumentation Laboratory, Werfen, Bedford, MA, USA). This assay is based on the homogeneous particle-enhanced turbidimetric immunoassay method. For each study point, 3 mL of saline were drawn from the fluid container and vancomycin measurement was done in triplicate.

Parameters and Isotherm Calculation

The following equation was used to calculate the removal ratio (RR) of vancomycin at each time-point:

$$RR_t(\%) = 100\ (C_0 - C_t)/C_0$$

where C_0 is the concentration at baseline, and C_t is the concentration at a defined time-point. Overall vancomycin mass ($Mass_{vanc}$) in the batch was calculated in milligrams as follows:

$$Mass_{vanc} = C\ V$$

where C was the concentration (mg/100 mL), V was the volume of the solution batch (mL).

Overall removal ratio (RR) was calculated using the formula:

$$RR = C_{end}/C_0$$

where C_{end} and C_0 were the concentrations of vancomycin in the batch 5 min after injection and at the end of the experiment (end) or right after a new bolus injection.

The mass adsorbed was calculated using the equation:

$$Mass_{adsorbed} = RR_t\ Mass_{injected}$$

for each sample time.

If we consider our system as a model characterized by a monolayer adsorption with a fixed number of localized sites, identical and equivalent, Langmuir adsorption isotherm can be applied to describe it:

$$\eta_{eq} = \frac{Q_0\ b\ c_e}{1 + b\ c_e}$$

where Q_0 and b are constants, c_e represents the equilibrium concentration of the compound to be adsorbed in the fluid phase and η_{eq} is the equilibrium load of the compound which is adsorbed onto the solid medium.

Referring to the adsorption of vancomycin on a bed of solid beads trapped into a suitable cartridge, Langmuir equation can be modified as follows:

$$\eta_{end} = \frac{Q_0\ b\ m_o}{1 + b\ m_0}$$

where Q_0 and b are always constants, m_0 represents the initial amount of vancomycin load in the accumulation vessel (mg) and η_{end} is the final load of vancomycin which is adsorbed onto the solid beads (mg/g).

Results

In vitro experiments confirm the affinity of beads material in binding vancomycin molecules. In all the HP simulations, the antibiotic has been adsorbed in significant amount. In the preliminary tests, the error between the measured concentration and the expected concentration based on injection quantity in affixed batch of saline was marginal, as demonstrated by the Bland-Altman plot in Figure 3.

Protocol a

A total amount of 700 mg and 900 mg of vancomycin was injected in two different experiments with repeated boluses of 100 mg after at least 20 min from one to an-

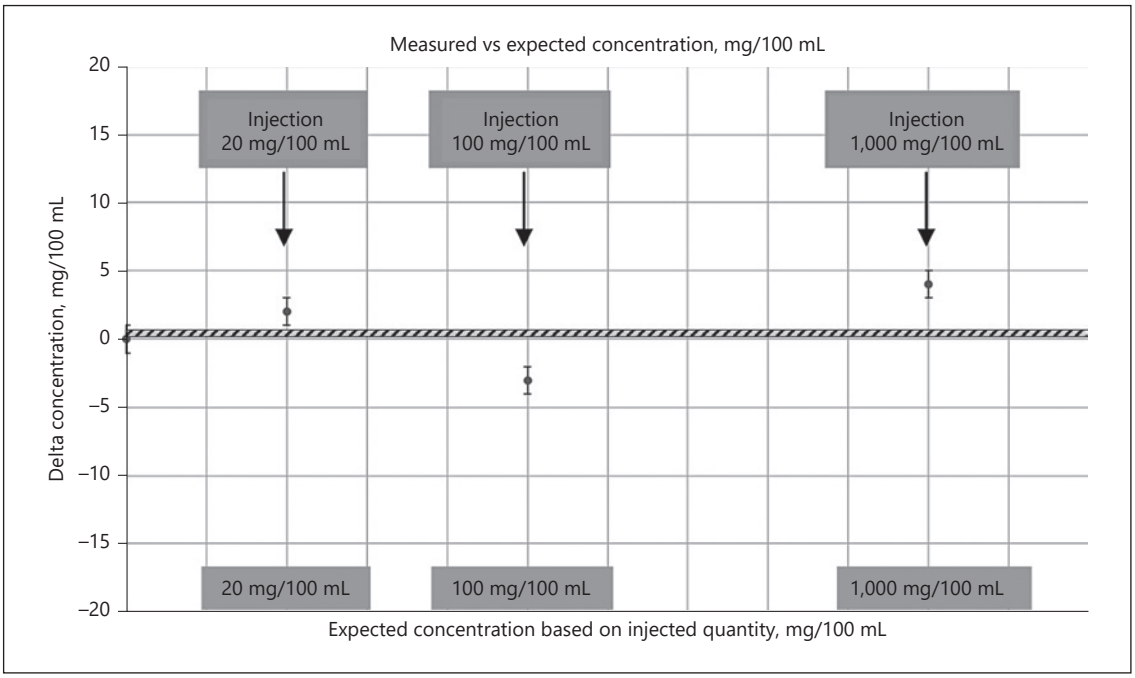

Fig. 3. Bland-Altman plot shows the error between the measured concentration and the expected concentration based on injection quantity in affixed batch of saline solution.

Table 1. Data for vancomycin removal and equilibrium load

Mass injected, mg	Mass adsorbed, mg	Circulation time, min	Circulating volume, mL	Equilibrium load, mg/g
100	98	20	5,000	3.90
200	191	20	5,000	7.62
300	284	30	7,500	11.37
400	377	30	7,500	15.07
500	468	40	10,000	18.71
600	556	40	10,000	22.24
700	646	40	10,000	25.83
600	580	80	20,000	23.22
700	673	80	20,000	26.90
800	765	80	20,000	30.61
900	851	80	20,000	34.05
5,000	4,689	300	75,000	187.54
10,000	6,111	300	75,000	244.44

other. The RRs 20 min after injections were higher than 80% in all the repetitions. Increasing the total amount injected in the reservoir (600 mg or higher), we observed a progressive reduction in the speed of adsorption as demonstrated by the progressive increase of the time necessary to reach the adsorption equilibrium (see Table 1). Eighty min of circulation were necessary to reach a RR higher than 90%. At the end of the two experiments, the total masses adsorbed were 650 mg of 700 mg injected and 840 mg of 900 mg injected. The RRs were 92% and 94%, respectively.

Protocol b

In the second experimental approach, 500 mL and 1,000 mL of saline solution enriched with 5,000 mg and 10,000 mg of vancomycin circulated through the car-

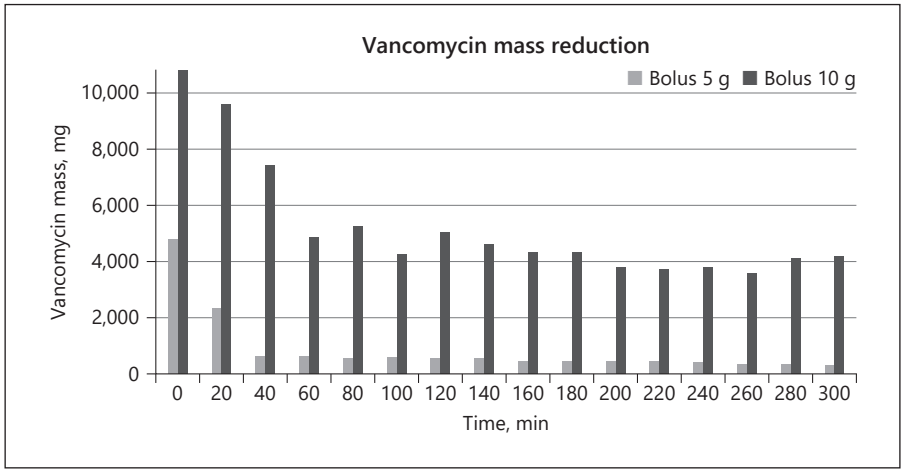

Fig. 4. Vancomycin mass variation in the reservoir during HP simulation with HA380 mini-modules. Circulating solutions were enriched with 5,000 mg and 10,000 mg of vancomycin.

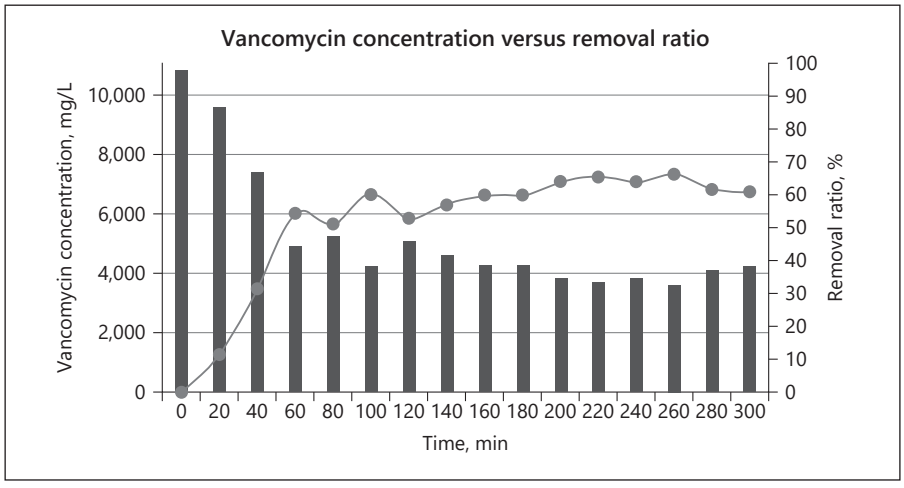

Fig. 5. Vancomycin concentrations decrease (vertical bars) compared to the removal ratio curve (data referred to 10 g of vancomycin in 1 L of saline solution).

tridge. The kinetics of vancomycin adsorption is characterized by a rapid exponential decay of solute concentration in the batch in the early phases of the experiments. Afterward, the curve approximates a plateau (Fig. 4). 4,689 mg of the 5,000 mg injected were adsorbed at the end of the experiment (RR = 94%), of which 90% in the first 40 min (RR = 87%); after this period, the curve became flat, and the adsorption phenomenon was negligible.

In the experiment with 10,000 mg, after 60 min of rapid adsorption (RR = 55%), the curve reached a plateau resulting in a final RR slightly higher than 60% (Fig. 5). The sorbent was able to bind 6,100 mg of the 10,000 mg injected. Experimental data have been leveraged to infer the Langmuir isotherm model describing our system. Table 1 reports data collected for vancomycin adsorption on the beads.

The resulting experimental isotherm together with the best fit for a Langmuir expression is reported in Figure 6. Trying to fit the data using Langmuir isotherm leads to the following parameters: $Q_0 = 524.6$, $b = 930.5 \times 10^3$. As it is possible to notice from the obtained fitting parameters, Q_0 physically expressed the maximum equilibrium load at very high injected mass of vancomycin.

Discussion/Conclusion

The experiments allowed us to calculate the maximal amount of vancomycin that can be absorbed on the neutro-macroporous resin per gram of sorbent substrate. In particular, given the amount of dry resin in the mini-module (25 g), we can infer that a maximum of 244 mg of vancomycin can be adsorbed per gram of sorbent. Con-

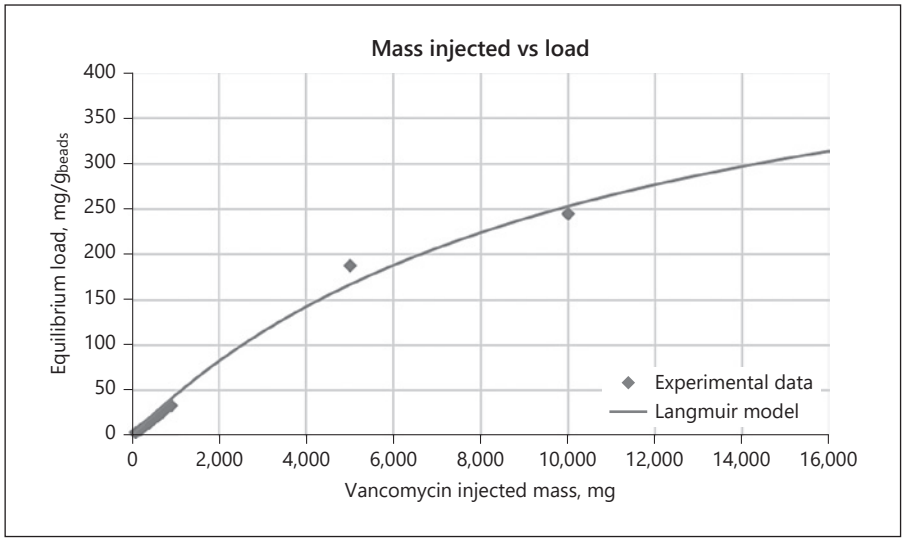

Fig. 6. Vancomycin on solid beads adsorption experimental data and best fit with a Langmuir isotherm.

sidering that the mini-module contains ¼ the amount of HA380 resin, we can conclude that approximately 24 g of vancomycin can be adsorbed by a full-scale HA380 cartridge used in clinical hemoperfusion. One may speculate that the flow conditions and the presence of a different fluid phase such as full blood in vivo may modify the times and the modality of adsorption as well as the total quantity of antibiotic required to saturate the cartridge. However, even assuming a negative interference by plasma proteins and other blood components, a modified flow-dynamic pattern inside a bigger cartridge, and a possible reduction of 50% of the adsorption capacity due to channeling phenomena, the overall amount of vancomycin required to saturate the cartridge is higher than 10 g. In reality, previous studies have demonstrated that, independent of the blood flow and the size of the cartridge, the flow distribution inside the devices and through the sorbent bed is homogeneous with complete utilization of the interparticle space [20]. This is favored by the particle diameter (fairly constant) and the packing density of the sorbent beads that remains always below 50% of the available space. This means that in a critically ill patient who receives 2 g/24 h, as an effective vancomycin treatment, the level of antibiotic in the blood during hemoperfusion may reach values close to zero and adequate supplementation should be considered in light of the high removal capacity of the extracorporeal therapy.

Instantaneous adsorption clearance K_a can be measured in the system with the following equation:

$$K_a = Q\,(C_i - C_o) / C_i$$

where C_i and C_o are the concentrations measured at the inlet and the outlet of the sorbent cartridge and Q is the flow through the cartridge. Since no filtration occurs in the cartridge, the flow is constant before and after the unit. Thus, the final concentration will be characterized by a negative exponential curve, with maximal removal in the early phases of the experiment and minimal (close to zero) at the end of the experiment when full saturation of the sorbent has occurred.

In vivo, further factors are involved such as the presence of blood and its viscosity, the volume of distribution of the drug in vascular and extravascular compartments, the constant of transport between different compartments, and the proportional protein binding.

An important aspect is also related to the physical configuration of the sorbent unit and the flow distribution inside the sorbent bed. In particular, the tortuous path of the fluid phase (blood) in the interparticle space must be optimized in order to avoid channeling phenomena and dishomogeneous utilization of the sorbent material. This is normally studied with dye injection and CT scan analysis of the internal flow distribution at different flows, as well as with the evaluation of the mass transfer zone inside the sorbent bed.

Adsorption isotherms can be used to determine the amount of adsorbent required to remove a given amount of solute from the solvent. Nevertheless, isotherms may be different in case of different unit design [21]. This depends on the packing density of the sorbent, the length and inner diameter of the unit (cartridge), the interparticle distance, and path tortuosity, the flow dynamics in-

side the unit. The flow characteristics through a sorbent bed are governed by physical laws such as the Darcy's law and the Cozeny-Karman equation that however go beyond the scope of this paper. In practice, however, the adequacy of unit design can be evaluated by measuring the solute mass transfer zone (MTZ) inside the unit. At different times of the experiment, the MTZ (expressed in cm) is represented by the distance between the point (cross section) where all sorbent material is saturated and the point at which zero adsorbate is present on the sorbent. Depending on flow distribution inside the unit, MTZ may be very short (less than 1/3 of the unit length), may be equal to or longer than the unit length. In the last 2 cases, since the beginning of the isotherm curve determination, a flow through condition (i.e., a condition when solute is present at the outlet of the unit, leaving behind some sorbent mass not utilized for adsorption) is experienced [20]. The main problem is to obtain the maximum contact of the fluid phase with the entire amount of available sorbent. There are various steps in the adsorption process: external (interphase) mass transfer of the solute from the bulk fluid by convection through a thin film or boundary layer, to the outer surface of the sorbent; the internal (intraphase) mass transfer of the solute by pore diffusion from the outer surface of the adsorbent to the inner surface of the internal porous structure; the surface diffusion along the porous surface and finally the adsorption of the solute onto the porous surface. During clinical utilization, the final kinetics also depends on the extracorporeal blood flow and the initial concentration of the marker molecule. These factors may, in fact, result in earlier saturation or prolonged efficiency of the hemoperfusion unit [22].

From these calculations, two important conclusions can be drawn. (1) The dose of antibiotic currently prescribed in patients with severe infection or septic shock undergoing hemoperfusion treatment might have been insufficient to compensate for the rapid adsorption of the vancomycin during the first 2–4 h of extracorporeal circulation. This could in part explain some negative outcomes of patients treated with hemoperfusion in the past. (2) In the future, an accurate prescription of antibiotic therapy (at least in the case of vancomycin) should be made, taking into account the type of extracorporeal hemoperfusion device utilized, the hours of extracorporeal circulation, and the operational conditions applied to each specific patient. Further studies in the future should be directed to apply the same methodology as in this study to different molecules and different adsorption devices.

Acknowledgments

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Statement of Ethics

Ethics approval was not required for this study since we conducted an in vitro study and no patients were involved.

Conflict of Interest Statement

In the last 3 years, Claudio Ronco has received fees for lectures, advisory boards, consultation, and speaker bureau from ASAHI, ASTUTE, BAXTER, B. BRAUN, Biomerieux, CYTOSORBENTS, FMC, GE, JAFRON, Medtronic, Ortho, ESTOR, and TORAY. Anna Lorenzin, Massimo de Cal, Matteo Marcello, David Sorbo, Sabrina Copelli, Silvia de Rosa, and Monica Zanella have no COI to disclose.

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Author Contributions

Anna Lorenzin, Massimo de Cal, Matteo Marcello, and Claudio Ronco contributed in the study design and in the experimental settings. Massimo de Cal contributed in the sample measurements. Anna Lorenzin and Sabrina Copelli contributed in the data analysis. Anna Lorenzin, Massimo de Cal, Matteo Marcello, David Sorbo, Sabrina Copelli, Claudio Ronco, Silvia de Rosa, and Monica Zanella contributed in the interpretation and the writing process. All the authors revised critically the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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