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Brief Report

Removal of ticagrelor by hemoadsorption with the HA380 cartridge

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Short Title: Ticagrelor hemoadsorption

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Abstract

Introduction: Hemoadsorption has emerged as a potential intervention for the removal of ticagrelor. We aimed to evaluate the efficacy of the HA380 hemoadsorption cartridge for this purpose.

Methods: Six healthy adult sheep received 270 mg of ticagrelor via an orogastric tube, followed by hemoadsorption using a HA380 cartridge for a duration of 4 hours. The sorbent-based removal ratio, clearance, and mass removal rate were assessed at multiple time points.

Results: The HA380 cartridge achieved an initial sorbent-based removal ratio of 48.9% (SD 11.8) at 10 minutes, which declined rapidly to 2.66% (SD 18.5) at 120 minutes and 0.48% (SD 17.0) at 240 minutes. Clearance followed a similar trend, starting at 46.1 mL/min (SD 11.4) and decreasing to 0.08

mL/min (SD 16.8) at 240 minutes. The mass removal rate also dropped significantly over time, from 3.74 ng/min (SD 2.54) at 10 minutes to near zero at 120 and 240 minutes.

Conclusion: HA with the HA380 cartridge can achieves an early 50% adsorption level for ticagrelor. If frequently changed, the HA380 cartridge may serve as a potential option for ticagrelor removal, when clinically indicated.

Introduction

Ticagrelor, an antiplatelet drug that acts as a reversible and direct-acting inhibitor of the adenosine diphosphate P2Y12 receptor, is widely prescribed for coronary artery disease.[1] However, managing ticagrelor in the context of life-threatening bleeding or urgent surgery is extremely challenging due to the lack of drug reversal and/or removal strategies.

Hemoadsorption (HA) is emerging as a potential intervention in these scenarios as indicated by previous studies.[3–5] Hemoadsorption appears to remove ticagrelor from the plasma despite its high protein binding (>99%) leveraging its reversible binding to the P2Y12 receptor.[2] However, current evidence indicates significant variability in drug removal performance across different cartridges used for HA.[6]

The HA series (Jafron Biomedical, Zhuhai, China) is a novel group of cartridges designed for HA.[7] While these cartridges have been used for the treatment of drug intoxication [8–11], their efficacy in removing ticagrelor has not been investigated.

Materials and Methods

Experimental protocol

Six sheep were studied under general anesthesia induced with propofol (4 mg/kg; I.V, Feresofol®, Fresenius Kabi Australia, NSW, Australia) and fentanyl (5 µg/kg I.V. , Fentanyl GH, Panpharma, Trittau, Germany), and maintained with sevoflurane (2–4%, Piramal Sevoflurane®, Piramal Critical Care, Pennsylvania, USA), propofol (4 mg/kg/h; I.V), and fentanyl (3 µg/kg/h; I.V). Following the induction of general anesthesia, ticagrelor (270 mg, Brilinta, AstraZeneca, Sydney, Australia) was given via an orogastric tube.

After 75 min, HA was initiated and performed for a total duration of 4 h, using a HA380 cartridge, a dedicated device (TR-525®, Toray Medical, Tokyo, Japan) and circuit (JCH-55X2-CHDF-2®, Toray Medical, Tokyo, Japan). The extracorporeal circuits were prepared according to the manufacturer's instructions, as previously described.[12] The blood flow rate was initially set at 30 mL/min and gradually increased over a period of 10 minutes to 120 mL/min. Heparin (Heparin Injection®; Pfizer, Sydney, Australia) was given for anticoagulation as a bolus of 3,000 IU followed by a continuous infusion of 2,000 IU/h until the end of experiment.

Blood samples and analysis

Blood samples were collected 30, 60, and 75 minutes after drug administration. After the initiation of HA, additional samples were collected at 10, 30, 60, 120, and 240 min from two different ports located before and after the cartridge. Blood hemoglobin levels were measured using ABL Systems 625 (Copenhagen, Denmark). Plasma concentrations of ticagrelor were quantified by high performance liquid chromatography with tandem mass spectrometry.[13] Isotopically labelled internal standards were used for quantification to circumvent the matrix effect variability.

Experimental measurements

We calculated the sorbent-based removal ratio (RR), clearance (CL), and mass removal rate (V_{rem}) for each time point using the following formulas as previously reported[12]:

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

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

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

C_{pre} and C_{post} represent the drug concentrations in the pre- and post-cartridge samples, respectively. Q_p refers to the effective plasma flow, calculated as the product of the blood flow and (1 minus the hematocrit). Hematocrit was estimated by multiplying the hemoglobin by a factor of three.

Statistical analysis

Data are presented as means with SDs. Statistical analysis was conducted using GraphPad Prism® for Windows, version 10 (GraphPad Software, Boston, USA). Data were subjected to one-way repeated measures ANOVA with a Greenhouse–Geisser correction applied to the main effect of time. Within-animal comparisons between the 10-minute timepoint and each timepoint were performed using Dunnett's test. A two-sided p-value ≤ 0.05 was considered statistically significant.

Results

Plasma concentrations, the calculated sorbent-based RRs, CLs and V_{rem} of ticagrelor are shown in Figure 1. The sorbent-based RR of ticagrelor was 48.9% (SD 11.8) at 10 minutes, decreasing rapidly over time (P_{time} = 0.0045, Figure 1b). By 120 minutes, the RR had dropped to 2.66% (SD 18.5), and it further declined by 240 min to 0.48% (SD 17.0).

The sorbent-based CL changed proportionally to the RR as Q_p remained relatively stable. CL decreased over time (P_{time} = 0.0058), starting at 46.1 mL/min (SD 11.4) and reaching nearly zero by 120 minutes, with the final CL at 240 minutes at 0.08 mL/min (SD 16.8, Figure 1c). The sorbent-based V_{rem} also exhibited a decrease over the 4-h procedure (P_{time} = 0.0097), from 3.74 ng/min (SD 2.54) at 10 min to close to zero at 120 and 240 mins (Figure 1d).

Discussion

In anesthetized healthy sheep, the HA380 cartridge initially achieved a RR of approximately 50% for ticagrelor. This RR progressively and rapidly declined, reaching nearly zero by 120 minutes after HA initiation.

To our knowledge, this study is the first to assess the impact of HA using HA380 cartridges on ticagrelor removal. A previous *in vitro* study demonstrated substantial removal of ticagrelor using CytoSorb®.[3] However, *in vitro* adsorption does not reflect *in vivo* performance [14]. Nonetheless, HA with CytoSorb® may reduce bleeding complications in emergency cardiac surgery requiring cardiopulmonary bypass [4], and registry studies and clinical trials are currently underway.[15,16] Moreover, the European Society of Cardiology recommends considering HA in patients on ticagrelor requiring emergency cardiac surgery.[17] Our findings suggest the Jafron HA380 may also have utility in this setting. However, removal of ticagrelor beyond 2 hours is low and less than for other drugs, possibly because of its higher protein binding.[2,18,19] Desorption remains a concern with these techniques as noted with CytoSorb® cartridges.[20]. Thus, our findings indicate that HA380 cartridges can achieve early removal of ticagrelor and suggest that hourly cartridge changes may be desirable. Investigations of this cartridge with frequent changes are now required and justified in clinically relevant scenarios such as during cardiopulmonary bypass.

We acknowledge several limitations. Firstly, we used young, healthy animals, whereas patients requiring urgent ticagrelor removal often present with varying degrees of organ dysfunction. Second, we did not assess platelet function. However, previous studies have shown that plasma concentrations of ticagrelor closely correlate with inhibition of platelet aggregation.[2] Thirdly, this experiment lacked a blank control. Typically, ticagrelor reaches its peak blood concentration orally within 2 to 3 hours. However, the experiment commenced while the ticagrelor concentration was still potentially increasing, prior to reaching its peak. This timing could have impacted both the adsorber's drug clearance capacity and the precision of the calculations. Lastly, higher blood flow rates may achieve greater removal but could not be delivered in a 40 kg sheep.

In summary, HA with the HA380 cartridge achieves 50% adsorption of ticagrelor. This suggests that the HA380 cartridge, combined with frequent change, could serve as a potential option for ticagrelor removal when clinically indicated. Further clinical studies are required and justified in the clinical setting.

Statements

Acknowledgement

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Statement of Ethics

All procedures were approved by the Animal Ethics Committee of the Florey Institute of Neuroscience and Mental Health (approval number 22-028-FINMH) in accordance with the guidelines of the National Health and Medical Research Council of Australia. The study adhered to the Animal Research: Reporting of In Vivo Experiments (ARRIVE) criteria.

Conflict of Interest Statement

Rinaldo Bellomo has received payment from Jafron Biomedical as a member of the Medical Advisory Board and consultancy fees as speaker at several meetings. Rinaldo Bellomo, Ian Baldwin and Antoine Schneider were all members of the journal's Editorial Board at the time of submission.

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Author Contributions

TF, YRL, IB, CPCO, CNM and RB conceived and designed the research; TF, IB and SH performed the experiments. YD, AS and LAD supervised pharmacological analyses. TF analyzed data; TF, YRL and RB interpreted the data. TF drafted the manuscript. All authors edited and revised the manuscript and approved the final version.

Data Availability Statement

The data supporting the findings of this study are not publicly available due to ethical considerations. However, they are available by the corresponding author (RB) upon reasonable request.

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Figure Legends

Figure 1. Effects of HA on ticagrelor. **a** plasma concentration of ticagrelor. **b**, Sorbent-based RR. **c** Sorbent-based CL. **d** V_{rem}. Data are presented 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 < 0.01 (post hoc Dunnett's test) for comparison with the 10-min after initiation of HA. Abbreviation: CL, clearance; HA, hemoadsorption; RR, removal ratio; V_{rem}, mass removal rate.