Role of dual versus selective endothelin receptor antagonism in the prevention of axitinib-induced cardiovascular haemodynamic changes in conscious, freely-moving rats

Patrizia Pannucci, Julie March, Samantha Cooper, Stephen Hill and Jeanette Woolard
Division of Physiology, Pharmacology and Neuroscience, School of Life Sciences, University of Nottingham, Nottingham, NG7 2UH
Centre of Membrane Proteins and Receptors, University of Nottingham

University of Nottingham
UK | CHINA | MALAYSIA

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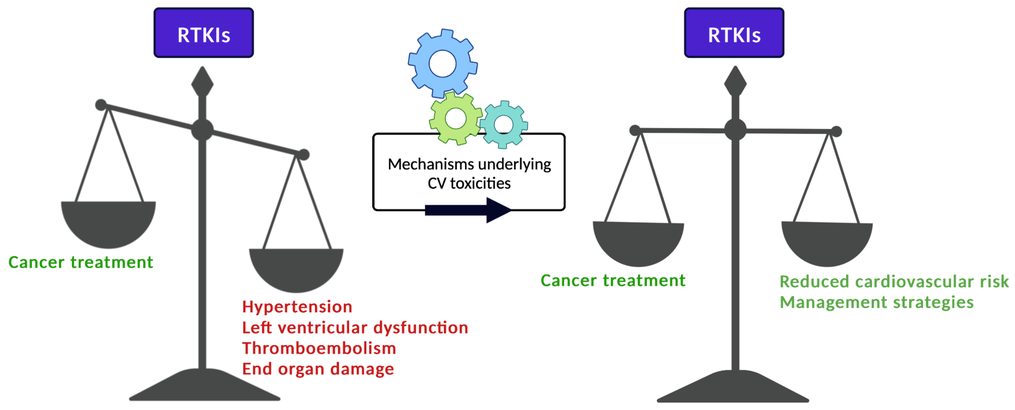
Introduction

Antiangiogenic therapies, targeting vascular endothelial growth factor receptors (VEGFRs), are a novel therapeutic approach in oncology. Along with the improved clinical outcomes associated with these therapies, unanticipated cardiotoxicities have emerged, in particular hypertension, often leading to temporary or permanent treatment discontinuation [1]. While the clinical cardiovascular manifestations of these drugs are unequivocal, the mechanisms underpinning their impairment of cardiovascular function are still largely unknown [2].



Purpose

In light of the serious cardiotoxicities associated with VEGFR inhibitors, coupled with the lack of effective therapeutic strategies to manage these events, a comprehensive evaluation of their cardiovascular effects and the underlying mechanisms is urgently needed to limit the cardiovascular risk associated with these therapeutics. Considering the rise of plasma endothelin-1 levels in patients receiving these drugs, this study aims to define the role of endothelin receptor antagonism in the prevention of VEGFR inhibitors-induced haemodynamic responses.

Methods

Bosentan (dual ETA/ETB receptor antagonist; 15mg/kg/h), sitaxentan (selective ETA receptor antagonist; 5mg/kg/h) and vehicle were administered 1 hour prior the treatment with axitinib (VEGFRs inhibitor indicated for the treatment of mRCC; 3mg/kg/h), in conscious freely-moving rats. Male Sprague Dawley Rats (350-450g) were chronically implanted with pulsed Doppler flow probes (around descending abdominal aorta, renal and mesenteric arteries) and catheters (jugular vein and distal abdominal aorta) [3]. Haemodynamic parameters were measured over 2 days, before and after daily administration of axitinib. Endothelin-1 (0.1uM, 0.3uM and 1uM; i.v. bolus) was administered to all groups at the end of day 2 to verify whether the cardiovascular effects had been attenuated by the infusion of bosentan and sitaxentan.

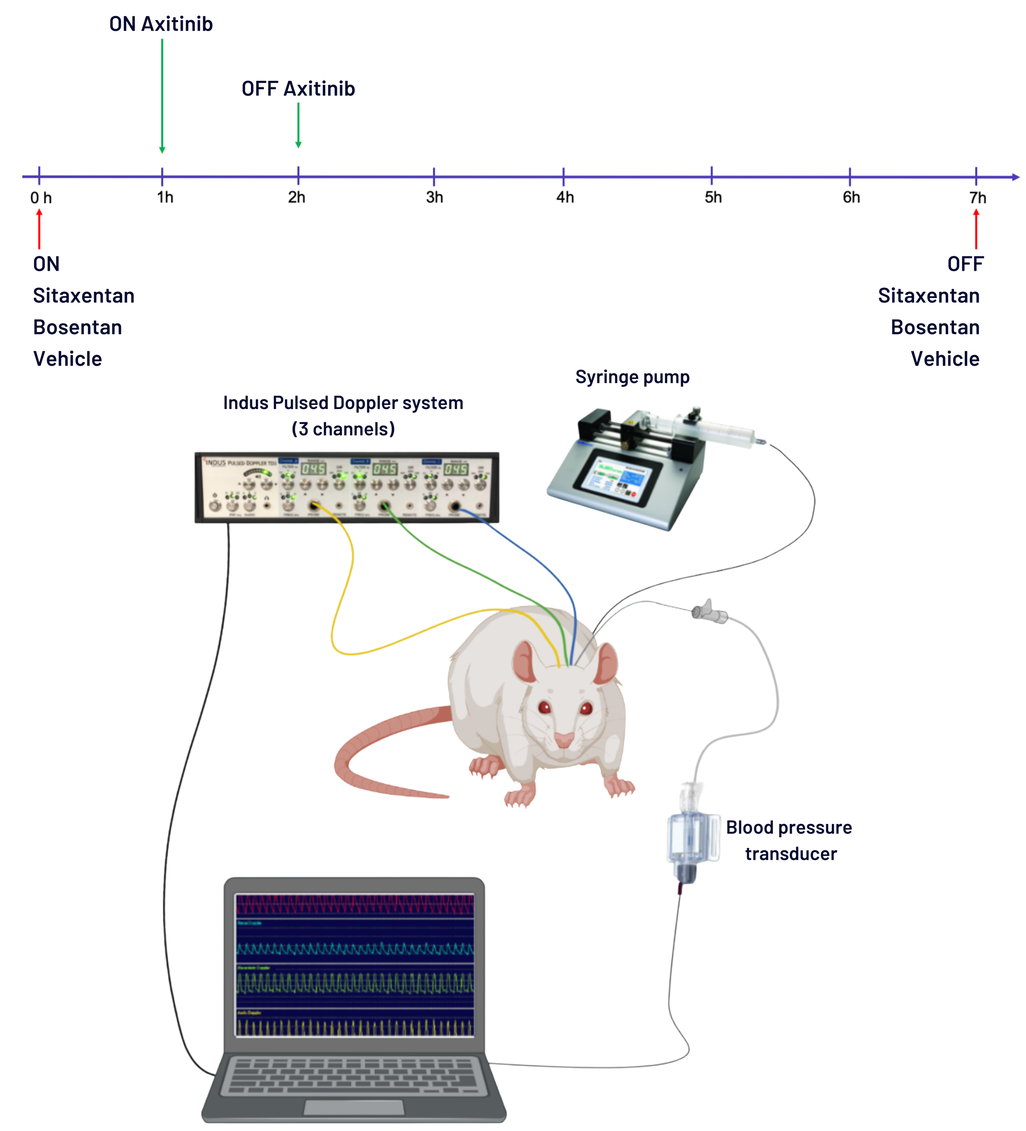


Figure 1: Schematic diagram of the experimental protocol used (top) and pulsed Doppler flowmetry setup (bottom).

Results

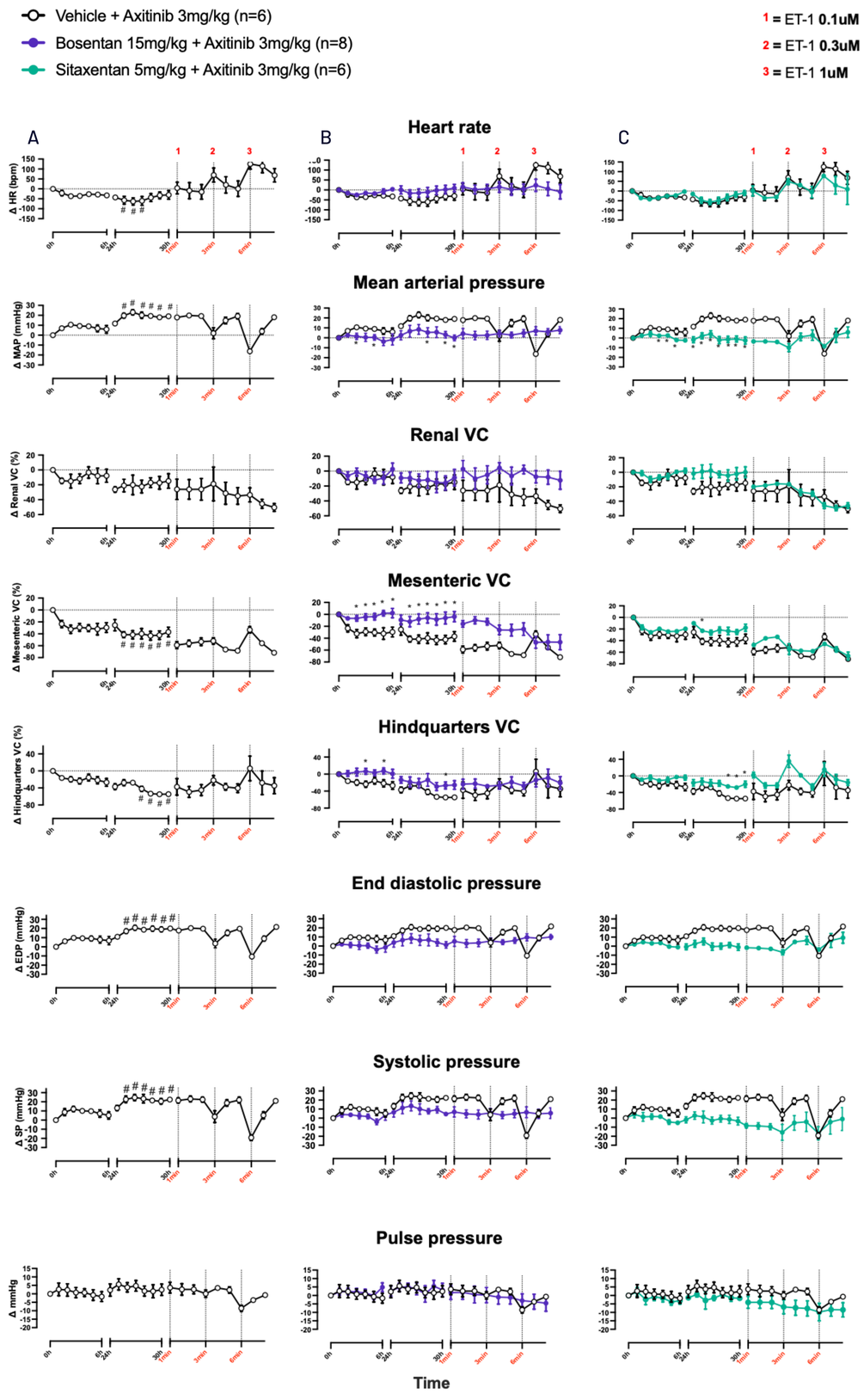


Figure 2: Selective antagonism of ETA receptor was sufficient to prevent axitinib-induced hypertensive effect.

Axitinib evoked a rapid and notable increase in mean arterial pressure, which was (23±3mmHg) compared to baseline (A). This pressor effect was accompanied by marked vasoconstrictions in the mesenteric and hindquarters vascular beds (A). Co-treatment with sitaxentan prevented the axitinib-induced hypertension more consistently than co-treatment with bosentan (B and C). The vasoconstrictions in mesenteric was reduced only in the bosentan co-treated group (B), while sitaxentan slightly blunted the axitinib-induced hindquarters vasoconstriction at the end of the second day period of treatment. Pre-treatment with sitaxentan antagonised the pressor effect of ET-1 and decreased the slope of ET-1 dose-response curve in hindquarters, at least at the lowest dose of ET-1, while renal and mesenteric vasoconstrictive responses to ET-1 still occurred (C).

Data shown represent mean ± S.E.M, with n numbers for each group indicated on the legend. * = $p<0.05$, Mann-Whitney U test (for comparison between vehicle and treated groups at each time point).

= $p<0.05$, Friedman Test (for within-group comparisons to baseline).

Conclusion

These preliminary results showed that the pressor effect induced by axitinib is primarily mediated by ETA receptor, as sitaxentan was more effective than bosentan in attenuating axitinib-induced hypertension. Therefore, selective ETA receptor antagonism may be a valid approach to prevent such side effect due to antiangiogenic therapies. Moreover, this study confirmed the powerful translational value of the Doppler Flowmetry model to detect and investigate the cardiovascular complications of these anticancer drugs.

Future work will assess the role of ET receptor antagonism in the prevention of hypertension induced by other VEGFR inhibitors; complementary *in vivo*, *ex vivo* and *in vitro* approaches will be used to provide additional mechanistic insights to RTKI-induced hypertension.

References

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2. Bair SM et al., (2013). Trends Cardiovasc Med23, 104-113.
3. Carter JJ et al., (2017). FASEB J 31, 1193-1203.

Acknowledgments

INSPIRE receives funding from the EU Horizon Research and Innovation programme, under the Marie Sklodowska-Curie Grant Agreement 858070.

The authors declare no conflicts of interest.