Effects of axitinib and lenvatinib on cardiovascular function and haemodynamic

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Introduction

The introduction of novel antiangiogenic treatments, targeting vascular endothelial growth factor receptors (VEGFRs), has changed the therapeutic approach in oncology. However, the clinical use of these targeted anticancer therapies has been associated with unanticipated cardiovascular complications (i.e., hypertension, left ventricular dysfunction and thromboembolism) [1]. Although this class of therapeutics strongly affects haemodynamic function in patients, the pathophysiological events behind the development of cardiovascular adverse effects induced by these therapies are still largely unknown, resulting in a reduction of therapeutic dosage or in a temporary or permanent treatment interruption [2].

Purpose

The severity of cardiovascular complications following the treatment with VEGFR inhibitors, along with the lack of antihypertensive strategies able to adequately manage these events, require an unequivocal and urgent assessment of their cardiovascular safety. This study aimed to determine the extent to which VEGFR inhibitors impact on cardiovascular function, profiling their effect on regional haemodynamic responses. Their cardiovascular assessment represents a valuable opportunity to investigate the mechanisms underlying cardiovascular toxicities induced by these novel antiangiogenic treatments.

Methodology

Male Sprague Dawley Rats (350-450 g) were chronically implanted under anaesthesia (fentanyl and medetomidine, 300 µg/kg i.p.of each) with pulsed Doppler flow probes (around the renal and mesenteric arteries, and the descending abdominal aorta) to measure Doppler shift, an index of vascular flow. After a 10-day recovery period, intravascular catheters were implanted in the jugular vein, for drug administration, and distal abdominal aorta to measure mean arterial pressure (MAP) and heart rate (HR) [3]. Haemodynamic parameters were measured over 4 days, before and after daily administration of axitinib (3 and 6 mg/kg, 3 and 6 mg/kg/h for 1 h, i.v.), or lenvatinib (3 and 6 mg/kg, 3 and 6 mg/kg/h for 1 h, i.v.). All experimental procedures were carried out with approval of the University of Nottingham Animal Welfare Ethical Review Board under Home Office Project and Personal License Authority.

Results

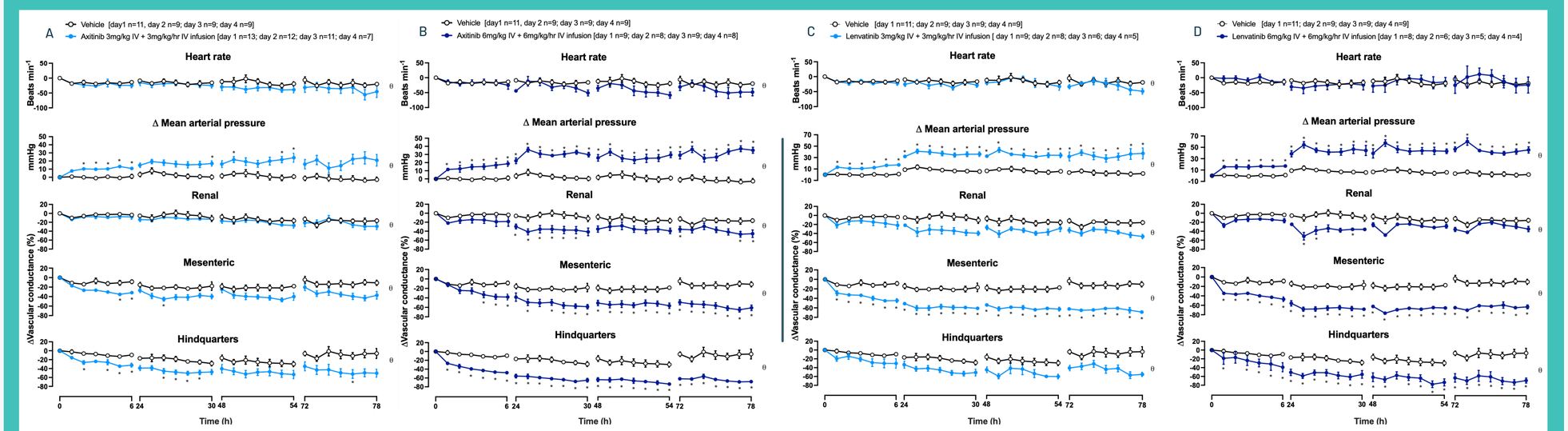
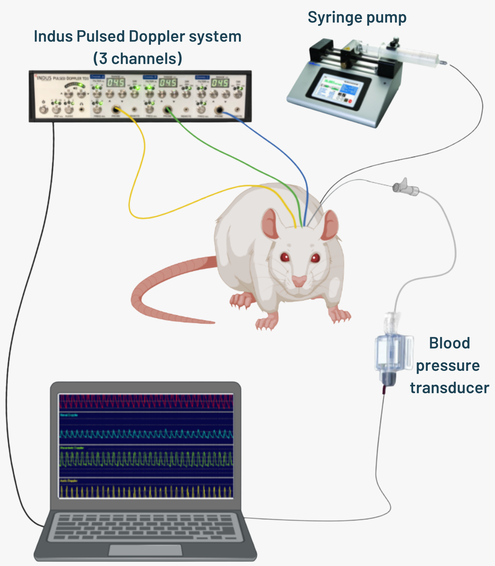


Figure 1: Both axitinib (A, B) and lenvatinib (C, D) evoked a significant hypertensive response, which, for axitinib 6 mg/kg (B) and lenvatinib 3mg/kg (C) and 6 mg/kg (D), progressively increased over the 4 days. This pressor effect was associated with a notable decrease of vascular conductance in the mesenteric (B, C, D) and hindquarters (B, D). Data shown represent mean ± S.E.M, with n numbers for each group indicated on the legend. * = P<0.05, Mann-Whitney U test (or comparison between vehicle and treated groups at each timepoint). Θ = P<0.05, Mann-Whitney U test, 0–78 h (for between-group comparison based on integrated area under or above curve analysis).



Conclusion

This study showed that the axitinib- and lenvatinib-induced hypertensive response is associated with regionally selective vasoconstrictions, which consistently occur in the hindquarters vascular bed. However, their vasoconstrictive profile differs in the renal and mesenteric vasculature. In addition, the Doppler flowmetry model showed to be a translational approach to predict the detrimental cardiovascular effects of these anticancer drugs, since the increase in blood pressure observed with this method reflects the hypertensive response reported in clinical practice. Having characterised the haemodynamic changes induced by axitinib and lenvatinib, the next approach will involve the assessment of the role of endothelin receptor antagonism in the control of such responses in order to elucidate the mechanisms underlying the cardiovascular complications induced by these anticancer therapies.

References

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