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Cardiovascular Effects of Multi-Targeted Receptor Tyrosine Kinase Inhibitors in Conscious Rats

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A major recent advance in cancer therapeutics has been the development of inhibitors of angiogenesis. Currently, several inhibitors of vascular endothelial growth factor (VEGF), including cediranib and sorafenib, are used as adjunct therapies to improve cancer prognosis [1]. An emerging issue with anti-VEGF therapies is the development of 'cardio-toxicity', initially producing significant hypertension and proteinuria (within 1-7 days), leading to left ventricular dysfunction and heart failure following longer-term exposure [2]. To gain more understanding of the mechanisms underlying the early hypertensive effects of anti-VEGF therapies, the present study has evaluated the regional haemodynamic effects of cediranib and sorafenib, in conscious, freely-moving rats.

Male, Sprague-Dawley rats (350-450g) were anaesthetized (fentanyl and medetomidine, 300 µg/kg i.p. of each) and implanted with pulsed Doppler flow probes and intravascular catheters (jugular vein, distal abdominal aorta) to measure renal (R), mesenteric (M) and hindquarters (H) vascular conductances (VC), in a two-stage procedure as described previously [3]. Experiments began 24h after catheterisation and ran over 4 days. On each day, vehicle (5% Propylene glycol, 2% Tween80, in saline, i.v.), cediranib (3 mg/kg; 3 mg/kg/h, i.v.), or sorafenib (10 mg/kg; 10 mg/kg/h, i.v.) was administered and measurements made for the following 4 h. Some of the data obtained are presented in Table 1.

Table 1: Changes in haemodynamic variables following administration of vehicle (Control), cediranib (3 mg/kg; 3 mg/kg/h) or sorafenib (10mg/kg; 10 mg/kg/h). Values are mean ± SEM. *P<0.05 vs. baseline (Friedman's test). $^{\#}$P<0.05 vs. sorafenib (Mann-Whitney U test).

	Control (n=8)		Cediranib (n=7)		Sorafenib (n=7)	
	4 h	**76 h**	**4 h**	**76 h**	**4 h**	**76 h**
ΔHR (beats min^{-1})	+1 ± 10	-20 ± 11*	-16 ± 7	-15 ± 10*	+3 ± 9	-17 ± 15*
ΔBP (mmHg)	-5 ± 2	-4 ± 3	+9 ± 3$^{\#}$	+36 ± 4*$^{\#}$	+6 ± 1	+12 ± 3*
RVC (%Δ)	+6 ± 15	+14 ± 17	-12 ± 4	-24 ± 9*	+2 ± 9	-11 ± 6
MVC (%Δ)	-2 ± 5	+10 ± 11	-29 ± 3*	-54 ± 4*$^{\#}$	-20 ± 5*	-22 ± 8*

HVC (%Δ)	-11 ± 4*	-14 ± 5	-22 ± 4*	-58 ± 4*#	-28 ± 4*	-36 ± 5*

Under control conditions resting cardiovascular variables (mean ± SEM) were: HR 372 ± 13 beats/min, BP 110 ± 3 mmHg, RVC 66 ± 8, MVC 77 ± 13, HVC 52 ± 3 (kHz/mmHg)10^3. Baseline values for the treated groups were not different to control. Cediranib and sorafenib evoked an increase in BP, together with mesenteric and hindquarters vasoconstrictions (Table 1). Cediranib caused a larger rise in BP compared to sorafenib, and the mesenteric and hindquarters vasoconstrictions were augmented. Cediranib also caused a renal vasoconstriction, an effect not observed with sorafenib. The results of this study recapitulate the observations made in the clinic and provide an experimental basis for a detailed evaluation of the mechanisms underlying these important cardiovascular side effects.

[1] Musumeci F et al, J Med Chem 55:10797, 2012.

[2] Vaklavas C et al, Oncologist 15:130, 2010.

[3] Fretwell LV & Woolard J, Br J Pharmacol 169:1279, 2013.