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Title: A dose-response study of nilotinib and imatinib in experimental pulmonary hypertension

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Body: Introduction: Platelet derived growth factor (PDGF) and c-kit are involved in the pathophysiology of pulmonary hypertension (PH). Tyrosine kinase inhibitor (TKI) targeting PDGF receptors and c-kit such as imatinib (Im) and nilotinib (Nil) are currently tested in PH. Aims and objectives:To test the efficacy of Nil and Im in experimental PH. Methods: Sprague-Dawley rats were analyzed, corresponding to controls (Cont), animals exposed to MCT, MCT and treated with Im at 50 or 100 mg/Kg/j (MCT+Im50-MCT+Im100), MCT and treated with Nil at 40, 80 or 120 mg/Kg/j (MCT+Nil40-MCT+Nil80-MCT+Nil120). TKI were administered from day 21 to 35 after MCT. Serum kinetics concentrations (SKC) of TKI were performed at day 28. At day 35 hemodynamic parameters, right cardiac hypertrophy and pulmonary vascular remodelling were studied. Results: SCK showed that Im50,Nil40 and Nil80 corresponded to human drug concentrations. A dose-response improvement in hemodynamic parameters and medial wall thickness was observed with Im and Nil.

Table 1

	Cont	MCT	MCT+Im50	MCT+Im100	MCT+Nil40	MCT+Nil80	MCT+Nil 120
RVSP(mmHg)	36,4±1,5	112,9±3,5**	96,0±6,1	85,3±8,43#	98,5±7,6	83,6±7,9##	83,8±6,0##
mPAP(mmHg)	14,7±0,7	47,5±0,9**	40,2±3,4	34,2±4,1#	42,7±3,1	35,0±3,0#	33,9±2,6##
CO(mL/min)	110,9±5,5	48,4±4,5**	89,8±6,9##	93,6±6,5##	88,2±8,3##	89,9±3,7###	93,4±6,4###
Fulton index	0,28±0,012	0,76±0,038***	0,59±0,037##	0,50±0,030##	0,67±00,068	0,55±0,031##	0,62±0,042#
	9.6±0.4	15.2±0.7***	12.2±0.5#	10.8±0.4###	11.4±0.4###	11.5±0.4###	10.7±0.4###

Medial wall thickness							

RVSP: Right ventricular systolic pressure, mPAP: mean pulmonary arterial pressure, CO: cardiac output, #p<0.05, ##p<0.005, ###p<0.001 vs MCT.

Conclusion: Dose-dependent improvements of experimental PH are observed with Nil and Im.