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ANTITHROMBOTIC DRUGS

PLATELET INHIBITION BY THE NOVEL NITRIC OXIDE-DONOR NITROSOOXYPROPANOL

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Introduction. The multiple roles of nitric oxide (NO) in human physiology include platelet inhibition and vasodilation, both important to prevent cardiovascular disease events like thrombosis and ischemia, common complications in cancer. NO-donating drugs, such as the clinically established nitroglycerine, have been used for decades, however, current NO-delivering therapies often suffer from limitations such as development of tolerance or the requirement for metabolic activation. The novel organic nitrite Nitrosooxypropanol (PDNO) has shown potent cardiovascular effects *in vivo* and preclinical studies have confirmed the safety and efficacy in models of acute pulmonary hypertension. Compared to conventional NO-donors, PDNO exhibits a superior pharmacological profile, marked by rapid onset and lack of tolerance. Due to PDNO's rapid release of bioavailable NO, treatment can be targeted to different vascular beds (depending on site of administration) and thereby reduce the risk of systemic side effects. Taken together, these properties position PDNO as an ideal candidate for drug repurposing beyond cardiopulmonary indications.

Aim. This project aims to elucidate the potential inhibitory capacity of PDNO on human platelets, which is yet unexplored and could be beneficial in new treatment strategies in indications of thrombosis.

Materials and Methods. Effects of PDNO on human platelet aggregation and secretion were investigated using impedance aggregometry in whole blood and light transmission aggregometry in platelet-rich plasma and isolated platelets. Molecular evidence was investigated by measuring cytosolic calcium mobilization and by western blot.

Results. Platelet aggregation and secretion induced by the thrombin receptor agonist SFLLRN was concentration-dependently inhibited by PDNO. Pharmacological comparison of platelet inhibition revealed that PDNO was more potent than the clinically used NO-donor nitroglycerin. Moreover, PDNO triggered NO/cGMP signaling, demonstrated by Ser239-specific phosphorylation of vasodilator-stimulated phosphoprotein (VASP). Measurements of cytosolic calcium showed that PDNO had similar capacity to reduce Ca^{2+} mobilization as the spontaneous NO-donor SNAP. The platelet inhibitory capacity of PDNO showed a rapid on-set of action and a surprisingly long-acting effect, from 10 seconds to 60 minutes.

Conclusions. The novel NO-donor PDNO elicits significant platelet inhibitory capacity and antithrombotic therapeutic potential.