A Hydrogen Sulfide Prodrug Augments Angiogenesis in a Swine Model of Critical Limb Ischemia via a Nitric Oxide Dependent Mechanism

Amanda M. Rushing, Amy L. Scarborough, Sarah F. Boisvert, Erminia Donnarumma, Rishi Trivedi, David J. Polhemus, David J. Lefer, and Traci T. Goodchild

Cardiovascular Center of Excellence, Louisiana State University Health Sciences Center, New Orleans, LA, United States

Introduction: Despite advances in revascularization, treatments for critical limb ischemia (CLI) have been largely unsuccessful. Hydrogen sulfide (H₂S) and nitric oxide (NO), are endogenous gasotransmitters which exert potent vasodilatory and proangiogenic effects. Recent experimental evidence suggest that the proangiogenic effects of H₂S are mediated in part through the NO pathway. We sought to determine whether a novel H₂S prodrug, SG-1002 (Sulfagenix, Inc. Cleveland OH), increases NO production and promotes peripheral revascularization.

Methods: CLI was generated in Yucatan miniswine (n=17) via carotid cutdown and placement of an Amplatzer vascular plug deployed within a Viabahn stent positioned proximally in the external iliac artery. At day 7 post-CLI pigs, received daily placebo or SG-1002 (1600 mg PO). Cuff-pressures were measured weekly by ankle/brachial index (ABI). Plasma H₂S, H₂S metabolite sulfane sulfur (SS), and NO metabolite, nitrite (NO₂) were measured. At day 42 post-CLI, digital subtraction angiography (DSA) was performed and opacified vessels quantitated.

Results: ABI was reduced to 0 following CLI induction. ABI improved in both groups but continued to demonstrate persistent ischemia with values below 0.25 at day 42 and showed no difference between groups. Circulating H₂S levels were similar between groups. SS levels were increased from baseline to day 42 in SG-1002 treated pigs (p < 0.001) but remained unchanged in placebo treated animals. At day 42, SG-1002 treatment increase circulating NO₂ levels (p < 0.05) compared to placebo. There was an increase in NO₂ levels from baseline to day 42 in SG-1002 treated pigs (p < 0.05). DSA revealed an increase of CLI limb vessel number in SG-1002 treated pigs compared to placebo (p < 0.05).

Conclusions: Treatment with the H₂S prodrug, SG-1002, results in increased metabolites of H₂S and NO signaling. H₂S treatment increased vascular density in the setting of severe CLI in a clinical relevant swine model.