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

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Introduction: Despite advances in revascularization, treatments for critical limb ischemia (CLI) have been largely unsuccessful. Hydrogen sulfide (H_2S) and nitric oxide (NO), are endogenous gasotransmitters which exert potent vasodilatory and proangiogenic effects. Resent experimental evidence suggest that the proangiogenic effects of H_2S are medicated in part through the NO pathway. We sought to determine whether a novel H_2S 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 H_2S, H_2S metabolite sulfane sulfur (SS), and NO metabolite, nitrite (NO_2) 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 H_2S 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 NO_2 levels ($p < 0.05$) compared to placebo. There was an increase in NO_2 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 H_2S prodrug, SG-1002, results in increased metabolites of H_2S and NO signaling. H_2S treatment increased vascular density in the setting of severe CLI in a clinical relevant swine model.