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FROM THIENOPYRIDINES TO NITROSOTHIOLS: A NOVEL POTENTIAL MECHANISM OF THIENOPYRIDINES BIOACTIVITY

i2 Poster Contributions
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Background: Thienopyridines (T) are critical for treatment in patients undergoing PCI. There is unexplained variability in their level of platelet inhibition. Given T form an acidic aqueous solution, we investigated whether they form S-nitrosylated derivatives through their critical thiol group without metabolic transformation.

Methods: Ticlopidin, clopidogrel and prasugrel were crushed into aqueous solution and sodium nitrite, or albumin-SNO added to study thienopyridine-SNO formation. Fluorescence/Ozone-based chemiluminescence techniques were utilised to specifically detect free thiol and NO release from the SNO produced, respectively.

Results: All 3 thienopyridines formed SNO under laboratory conditions. Thienopyridine SNO formation was largely dependent on extent of free thiol and pH, with prasugrel-SNO being formed more readily. Thienopyridine-SNO readily participated in trans-nitrosation reactions with albumin and plasma protein typically attributable to SNO chemistry.

Conclusions: Thienopyridines form an acidic solution and have sufficient free thiol - ideal conditions for SNO formation directly from the prodrug A low pH is key to the efficiency of SNO formation. These in vitro conditions mimic conditions found on ingesting thienopyridines into the stomach - low pH and ample supply of nitrite. Thienopyridine SNO formation can occur and result in bioactivity without enzymatic biotransformation and may explain the pleiotropic vascular and platelet effects of these agents.

Fig. 1