THE FORMATION OF S-NITROSOTHIOLS FROM THIENOPYRIDINES INHIBIT PLATELET AGGREGATION WITHOUT BIOTRANSFORMATION: NOVEL MECHANISM OF ACTION?

i2 Poster Contributions
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Background: The potent anti-platelet thienopyridines (Ticlopidine, Clopidogrel and Prasugrel) are pro-drugs that require metabolism to exhibit a critical thiol group in the active form that binds to the P2Y12 platelet receptor to inhibit platelet activation and prevent thrombus formation. We investigated whether these thienopyridines participate in S-nitrosation (SNO) reactions via this thiol group. Thienopyridine-SNO might contribute to the reservoir of blood nitric oxide metabolites and exhibit anti-platelet behaviour.

Methods: Thienopyridine-SNO formation was investigated from ticlopidine, clopidogrel and prasugrel added to aqueous sodium nitrite or SNO donor agent (albumin-SNO). Ozone-based chemiluminescence techniques were utilised to specifically detect NO release from the SNO produced. Effects on platelet aggregation was monitored using light transmittance in a 96 well microplate assay.

Results: SNO derivatives formed directly from anionic nitrite in water under laboratory conditions without the need for prior metabolism of the drugs. Thienopyridine-SNO formation was dependent on pH (max at lower pH), duration of mixing and increased with nitrite concentration. Prasugrel-SNO was more favourably formed (p<0.01 compared to Clopidogrel-SNO) and the relative proportion of SNO remaining after 2 hours was significantly greater (117% v/s 14%(p<0.001). The SNO moiety readily participated in trans-nitrosation reactions with albumin and plasma. Thienopyridine-SNO showed effective inhibition of platelet aggregation, with prasugrel-SNO being more effective than clopidogrel-SNO (IC50 2.6μM v/s 82 μM) whereas native drug or nitrite controls were ineffective at inhibiting ADP-induced platelet aggregation.

Conclusions: Thienopyridine-derived SNO is formed directly from the respective base drug without the need for prior metabolism and therefore may be an important additional contributor to the pharmacological effectiveness of thienopyridines on platelet function.