NITRIC OXIDE DONATION FROM THE CINOD NAPROXINOD COUNTERACTS CYCLOOXYGENASE INHIBITION-DEPENDENT CONTRACTION IN HUMAN MAMMARY ARTERIES

ACC Poster Contributions
Georgia World Congress Center, Hall B5
Tuesday, March 16, 2010, 9:30 a.m.-10:30 a.m.

Session Title: Biomarkers and Vascular Disease 2
Abstract Category: Vascular Biology/Atherosclerosis/Thrombosis/Endothelium
Presentation Number: 1274-351

Authors: Manlio Bolla, Alessandra Poggi, Barbara Vergani, Guido Gelpi, Julio Padron, Daniela Miglietta, NicOx Research, Milan, Italy, NicOx SA, Sophia Antipolis, France

Background: Hypertension and osteoarthritis (OA) show frequent co-morbidity. Current treatment of OA with traditional NSAIDs and COX-2 inhibitors may predispose to increased risk of cardiovascular events and blood pressure destabilization. Hypertension is frequently associated with endothelial dysfunction, characterized by a defect in vascular biosynthesis and activity of nitric oxide (NO).

Naproxcinod is the first-in-class cyclooxygenase inhibiting nitric oxide donator (CINOD) designed to provide anti-inflammatory efficacy in OA from its metabolite naproxen while donating NO, which is intended to mitigate the NSAID-dependent side effects at vascular level.

The aim of this study was to evaluate the effect of NO donation by naproxcinod in the presence of cyclooxygenase (COX) inhibition in human isolated mammary arteries (hIMA).

Methods: Artery specimens were obtained from patients undergoing coronary artery bypass grafting and prepared as rings for isometric tone recording. Morphology was assessed by electron transmission microscopy.

Results: In pre-contracted hIMA, endothelium-dependent vasorelaxation (acetylcholine) was reduced in comparison to the endothelium-independent (sodium nitroprusside) response. Accordingly, electron microscopy showed cellular abnormalities such as intima hyperplasia and endothelial cell degeneration. Naproxcinod (10 nM - 100 μM) caused a NO-mediated concentration-dependent relaxation (Emax= -52.4±6.9%, p<0.05, n=6). Conversely, naproxen caused a slight but significant vasoconstriction (Emax=8±4%, p<0.05, n=6). In non-precontracted hIMA, naproxcinod and the selective COX-1 inhibitor SC-560 showed no effect on vascular tone, while naproxen (Emax=17±2.7%, n=12), ibuprofen (Emax=8.8±2.3%, n=4) and rofecoxib (Emax=6.8±1.7%, n=4) caused a mild but significant vasoconstriction (p<0.05).

Conclusions: NO donation from naproxcinod is able to counteract the contracting effects of COX-2 inhibition from NSAIDs in arteries from patients with endothelial dysfunction. These data provide mechanistic support to clinical studies showing a differentiated blood pressure profile for naproxcinod as compared to naproxen in OA patients.