Effects of JNJ-17333030, naratriptan and sumatriptan on human isolated coronary arteries

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Introduction
- Species differences in receptor homology or expression can lead to marked differences in responses between laboratory animals and humans, so there is a need for testing compounds on relevant human tissues where available.
- Coronary vasoconstriction, a known side effect of some drugs such as triptans, has been demonstrated in human isolated tissues (MaassenVanDenBrink et al., 1998).
- In the current study, the coronary vasoconstrictor potential of JNJ-17333030, a 5HT reuptake inhibitor/alpha 2 antagonist, was compared to that of naratriptan and sumatriptan in human isolated coronary arteries, from both visibly atherosclerotic and non-atherosclerotic vessels, as part of its safety evaluation.

Methods
Left anterior descending or right coronary arteries, with either visible or no visible atherosclerosis, were taken from four donors (2 male and 2 female) who died of non-cardiac disorders. Arteries were obtained from ethically approved organ procurement organisations. The absence or presence of atherosclerosis was visually determined and subsequently assessed histologically. Vessel rings, ~3mm long, were suspended on hooks in 10ml organ baths containing Krebs' physiological salt solution, gassed with 95% O2/5% CO2 and maintained at 37°C. Vessels were stretched to a passive tension of 15mN (1.5g) and viability was assessed by exposure to KCl (30mM). Following confirmation of vessel viability, the following protocol was used:

Results
Pathology
Pathological assessment of the visibly identified atherosclerotic vessels revealed severe thickening and/or the presence of either old atherosclerotic plaques or marked deposition of ground substance and fibroblasts, which may indicate that a plaque was present previously. In contrast, although mild intimal thickening was observed, no such pathology was seen in the non-atherosclerotic vessels.

Pharmacology
In all vessels, PGF$_2$α and KCI caused contractions. SP caused relaxations in most vessels, indicating that the endothelium was functional. SNP caused relaxations which, in the atherosclerotic vessels only, were below the level of PGF$_2$α pre-contraction, indicating that these vessels had inherent tone. The effects of all compounds were significantly different from vehicle.

Conclusions
In conclusion, JNJ-17333030 did not contract either atherosclerotic or non-atherosclerotic human coronary arteries, whereas both triptans did. The magnitude of the responses to all compounds tested was greater in non-atherosclerotic vessels, demonstrating that atherosclerotic vessels are less responsive, possibly as a consequence of arterial stiffness. In addition, this study has demonstrated that high quality and consistent data can be obtained with human isolated tissues using a small number of donors.

References