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

Sandra Williams[a], Bob Sheldrick[a], Thomas Steckler[b], David Gallacher[b] & Rob Towart[b]
[a]Asterand UK Ltd, 2 Orchard Road, Royston, Hertfordshire, SG8 5HD, UK . [b]Johnson & Johnson Pharmaceutical Research & Development, a Division of Janssen Pharmaceutica, Turnhoutseweg 30, B-2340 Beerse, Belgium

Introduction

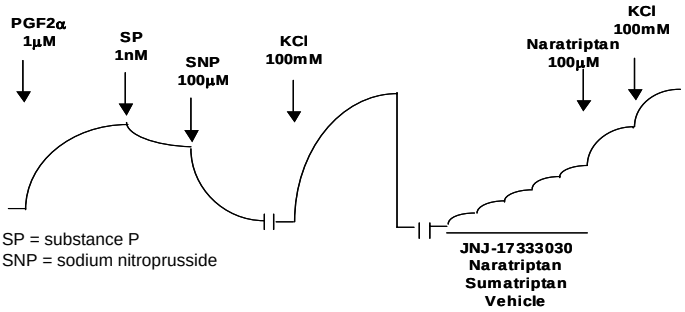
- Species differences in receptor homology or expression can lead to marked differences in responses between laboratory animals and humans, so there is a need for testing compounds on relevant human tissues where available.

- 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% O_2/5% CO_2 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:



SP = substance P
SNP = sodium nitroprusside

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.

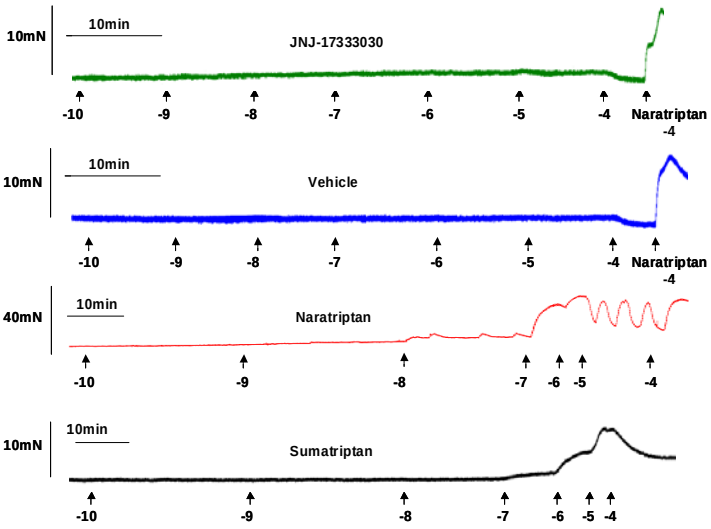
Pharmacology

In all vessels, $PGF_{2\alpha}$ and KCl 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 $PGF_{2\alpha}$ pre-contraction, indicating that these vessels had inherent tone. The effects of all compounds were greater in magnitude in the non-atherosclerotic vessels.

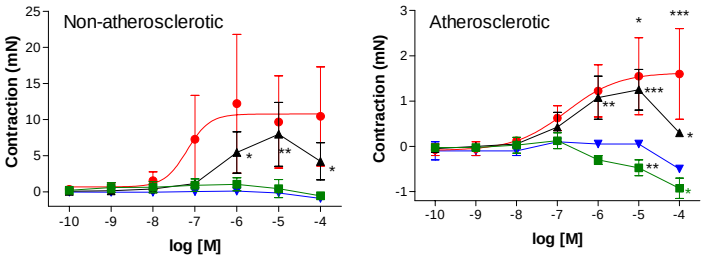
Vessel Type / Test Compounds	Non-atherosclerotic (n=16 tissues from 2 donors)	Atherosclerotic (n=12 tissues from 2 donors)
$PGF_{2\alpha}$ 1 μM (mN)	27.4 ± 2.9	5.3 ± 1.2***
Substance P 1nM (% $PGF_{2\alpha}$) [a]	*-37 ± 7*	*-20 ± 9*
SNP 100 μM (% $PGF_{2\alpha}$) [a]	*-104 ± 7*	*-197 ± 6***
Pre-treatment KCl 100 mM (mN)	28.9 ± 3.2	8.2 ± 0.9**
Post-treatment KCl 100 mM (mN)	32.5 ± 3.2	9.6 ± 1.1**

Data are mean ± s.e.m. [a] = response from $PGF_{2\alpha}$ pre-contraction
Significantly different from non-atherosclerotic ** =$P \leq 0.01$ *** = $P \leq 0.001$, two-way ANOVA test with Bonferroni post test

JNJ-17333030 did not contract human coronary arteries, whereas both triptans did.



Above figure shows original traces of the effects of JNJ-17333030, naratriptan, sumatriptan and vehicle in non-atherosclerotic vessels. Addition of naratriptan (10μM) to JNJ-17333030 and vehicle-treated vessels caused contractions in the majority of both atherosclerotic and non-atherosclerotic vessels. Concentrations are log M.



Graphical representation (above) and summary table (below) of concentration-effect curves to JNJ-17333030 (■), naratriptan (●), sumatriptan (▲) and vehicle (▼). Note different ordinate scales. Data are mean ± s.e.m (n = 3-4 vessels from 2 donors). Significantly different from vehicle * = $P \leq 0.05$, ** = $P \leq 0.01$, *** = $P \leq 0.001$, two-way ANOVA test with Bonferroni post test.

Treatment	Non-atherosclerotic		Atherosclerotic	
	pEC_{50}	max effect (% KCl 100mM)	pEC_{50}	max effect (% KCl 100mM)
JNJ-17333030	-	-5 ± 4	-	-11 ± 4
Vehicle	-	-4 ± 3	-	-4 ± 6
Naratriptan	7.2 ± 0.1	36 ± 19	6.8 ± 0.03	17 ± 10
Sumatriptan	6.2 ± 0.03	23 ± 1	6.7 ± 0.04	22 ± 13

Conclusions

In conclusion, JNJ-17333030 did not contract either atherosclerotic or non-atherosclerotic human coronary arteries, whereas both naratriptan and sumatriptan 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

MAASSENVANDENBRINK, A *et al* (1998). Coronary side-effect profiling of current and prospective antimigraine drugs. Circulation, **98**, 25-30