Effects of tegaserod on human isolated coronary arteries

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Introduction

- Tegaserod (Zelnorm®), a 5-HT_4 receptor agonist used for the treatment of irritable bowel syndrome, was recently suspended and subsequently withdrawn from the market due to a risk of serious cardiovascular adverse events e.g. angina, heart attacks and strokes[1].
- Coronary vasoconstriction, a known side effect of some drugs such as triptans[2] (which can increase the risk of a heart attack), has been demonstrated previously in human isolated tissues.
- A recent *in vitro* study showed tegaserod caused a variable vasoconstriction in canine but not porcine coronary arteries[3].
- In the current study, the constrictor potential of tegaserod was compared to sumatriptan and 5-HT in human isolated small and large coronary arteries (HCA) with or without atherosclerosis.

Methods

Hearts from 8 donors (4 male and 4 female, age range 20-75 years) who died of non-cardiac disorders were obtained from ethically approved organ procurement organisations. From these, left or right coronary arteries were dissected and cut into either small (sHCA, 0.3-0.5mm internal diameter (i.d.)) or large (LHCA, 1-2mm i.d.) vessel rings. The presence of atherosclerosis was confirmed histologically. Vessels rings were suspended in organ baths containing Krebs' physiological salt solution, gassed with 95% O_2 / 5% CO_2 and maintained at 37°C, and were either normalised to 100mmHg (sHCA) or stretched to a passive tension of 15mN (LHCA). Compounds were assessed either over a concentration range added cumulatively or at a single high concentration. Figure 1 summarises the protocol design.

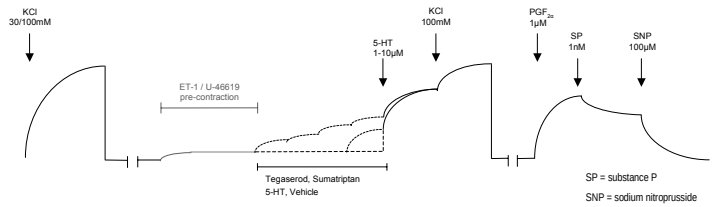

Figure 1. Schematic of experimental protocol

Endothelin (ET-1) or U-46619 pre-contraction (~20-35% of the KCl response), LHCA only.

Results

In all vessel rings, KCl, ET-1, U-46619 and $PGF_{2\alpha}$ caused contraction, whereas sodium nitroprusside caused relaxation; the response magnitudes were smaller (reduced by approximately 50%) in atherosclerotic vessels. Substance P caused relaxation in the majority of rings tested, demonstrating a functional endothelium [data not shown]. Sumatriptan and 5-HT caused concentration-dependent contractions that were similar in relative magnitude and potency in both sHCA and LHCA. Pre-contracting the vessels with either ET-1 or U-46619 had no effect on the magnitude of effect or potency of the test compounds (Table 1).

In non-atherosclerotic vessels, tegaserod caused a variable, transient contraction at high concentrations (10-100µM) in 4 out of 6 donors of LHCA and at lower concentrations (0.1-10µM) in 2 out of 3 donors of sHCA. Its vehicle, DMSO, caused clear relaxations at 10µM which might mask any contraction to tegaserod at this concentration (Figure 2 and Table 1). Similar responses were seen in atherosclerotic LHCA [data not shown].

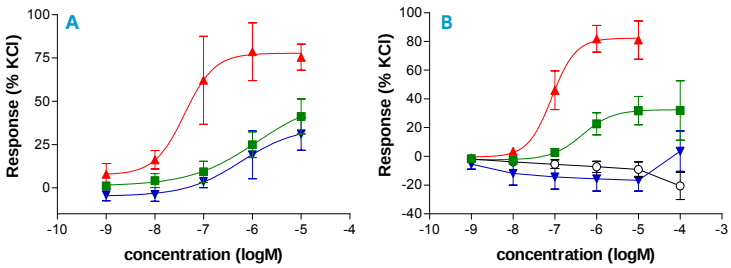

Figure 2. Graphical representation of concentration-effect curves to tegaserod (▼), sumatriptan (■), 5-HT (▲) and vehicle (○) in sHCA-basal tone (A) and non-atherosclerotic LHCA – ET-1 pre-contraction (B). Data expressed as a % of the final challenge to KCl (100mM).

Treatment CEC	sHCA			LHCA					
	Basal tone			ET-1 elevated tone			U-46619 elevated tone		
	pEC_{50}	E_{max}	(n)	pEC_{50}	E_{max}	(n)	pEC_{50}	E_{max}	(n)
Tegaserod	~6.4	31 (22-41)#	2	NC	4 ± 16	3	NC	-17 ± 30	3
Sumatriptan	6.4 ± 0.3	37 ± 11	4	6.3 ± 0.1	32 ± 11	5	6.5 ± 0.1	41 ± 28	3
5-HT	7.2 ± 0.3	84 ± 18	3	7.0 ± 0.2	83 ± 14	5	7.4 (7.3-7.4)#	104 (96-111)#	2
Vehicle	not-tested			-	-12 ± 8	5	-	-29 (-19 - -39)#	2

Table 1. Summary of results in non-atherosclerotic vessels. Data are mean ± s.e.mean (n = 3-5 donors), or #range (n = 2 donors). NC = non calculable. E_{max} = % KCl 100mM.

Tegaserod was subsequently tested only at a single high concentration (100µM) where clearer, but still variable, transient contractions were seen in 17/20 vessel rings from atherosclerotic LHCA (mean 55 ± 10%, range 4-129% of KCl). Vehicle caused small but variable relaxation. (Figure 3 and Table 2).

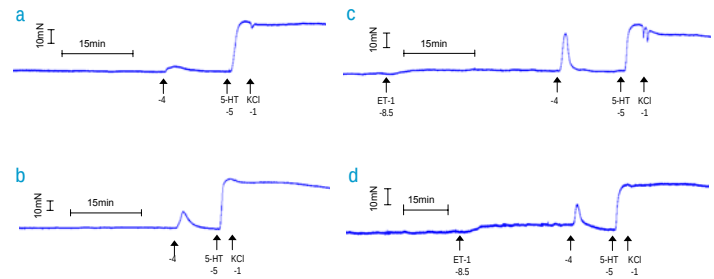

Figure 3. Example original traces of the effects of tegaserod. Tegaserod was tested at a single high concentration (100µM) on basal (a+b) and ET-1 pre-contracted (c+d) atherosclerotic LHCA from a 66 year old male donor. Concentrations are log M.

Donor	LHCA vessel rings		
	Pre-contracted ET-1	Responder / Total	E_{max} responders mean ± sem (% KCl)
1	2 / 4	4 / 4	52 ± 19
2	2 / 4	1 / 4	4
3	0 / 12	12 / 12	60 ± 13

Table 2. Effects of tegaserod (100µM) in atherosclerotic LHCA. E_{max} = % KCl 100mM, data are mean ± s.e.mean of responders (n = 4-12 rings per donor).

Discussion

- Tegaserod causes human coronary vasoconstriction, which is transient and variable in magnitude both within and across donors. Tegaserod appeared to be more potent in sHCA.
- Compared to sumatriptan, 5-HT was ~3-10-fold more potent and caused approximately double the contraction magnitude. The magnitude of effect and potency of both sumatriptan and 5-HT were independent of the size of the HCA or tonal level used.
- Further studies are ongoing to characterise the receptor(s) involved in mediating the coronary vasoconstrictor effect seen with tegaserod in this study.

References

[1]www.fda.gov/CDER/DRUGS/infopage/zelnorm/default.html [2]MAASSENVANDENBRINK, A *et al* (1998). Coronary side-effect profiling of current and prospective antimigraine drugs. Circulation, 98, 25-30

[3]BEATTIE D *et al* (2007). www.pa2online.org/abstract/abstract.jsp?abid=28928&author=beattie&cat=-1&period=33

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