

## Development of OCT2013, a hypoxia-activated prodrug of lidocaine, for the treatment of ischaemia-induced ventricular fibrillation

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**Introduction:** Sudden cardiac death (SCD) resulting from acute myocardial infarction (AMI) remains a substantial clinical burden, accounting for 50% of deaths from cardiovascular disease (1). Ischaemia-induced ventricular fibrillation (VF) is thought to be responsible for 80% of SCD related to AMI (2). Antiarrhythmic drugs are associated with dose-limiting adverse effects. OCT2013, a hypoxia-activated prodrug of lidocaine, has been synthesised and its effectiveness and safety were assessed in Langendorff-perfused rat hearts and in anaesthetised rats.

**Methods:** Male Wistar rat (295-400g) hearts were Langendorff-perfused with Krebs' (3mM K<sup>+</sup>) before left coronary artery (LAD) ligation (30mins). A switch of perfusate to vehicle, 15µM lidocaine or 15µM OCT2013 was made 10 mins before ligation (n=12), or, to vehicle, 15µM lidocaine, 60µM lidocaine, 15µM OCT2013 or 60µM OCT2013 10 mins after ligation (n=20). In both, the incidence of VF was recorded, plus ECG measures. Male Sprague Dawley rats (450-700g) were mechanically ventilated and anaesthetised with isoflurane+O<sub>2</sub> (1.5-2.5%, 90-100 breathes/min, 3-4mL). In one experiment, infusion of saline or 2mg.kg<sup>-1</sup> (+0.5mg.kg<sup>-1</sup>.min<sup>-1</sup>) lidocaine or OCT2013 (i.v.) began 5 mins prior to 30 mins LAD ligation (n=6). In another experiment (n=5), cardiac output (ml.min<sup>-1</sup>) was measured by left ventricular catheterisation. 1-32mg.kg<sup>-1</sup> OCT2013 or lidocaine was administered in a dose-doubling manner (i.v.). Incidence of VF was analysed via Fisher's exact test. Where appropriate, other data was analysed by two-way ANOVA followed by Dunnett's *post hoc* test. Significance was set at p<0.05. All experiments were blinded and randomised, in accordance with BJP guidelines (3).

**Results:** Lidocaine and OCT2013 were equi-effective at inhibiting VF, whether administered before (Fig 2A) or after ischaemia onset (Fig 2B) in Langendorff preparation. OCT2013 didn't induce dose-limiting bradycardia or PR interval elongation, in contrast with lidocaine (Figure 1A, 1B). Coronary ligation *in vivo* revealed similar antiarrhythmic effectiveness of OCT2013 and lidocaine via Kaplan Meier analysis (Fig 3A). In dose-doubling experiments in anaesthetised rats, cardiac output was significantly reduced by lidocaine, but unaltered by OCT2013 up to 32mg.kg<sup>-1</sup> (Fig 3B).

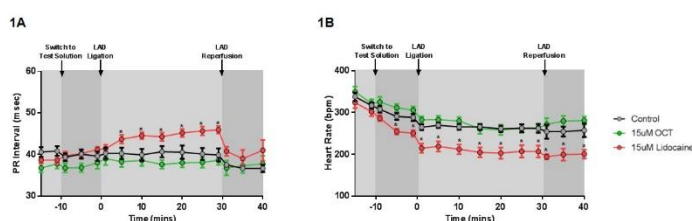


Figure 1) A. PR interval (ms) and B. Heart rate (bpm), at baseline, following solution switch and following LAD ligation (30 mins) and reperfusion (10 mins). 2 way ANOVA with Dunnett's *post hoc* test. \*P<0.05 (s) vs control, n=12/group. Values are mean± SEM

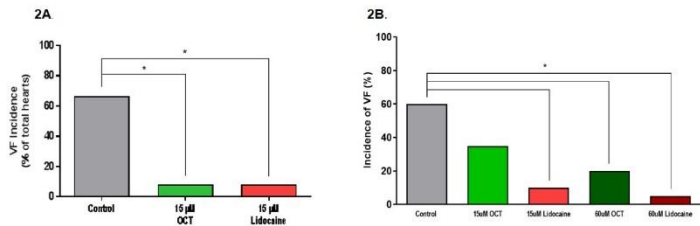


Figure 2) **A.** VF incidence (%) during 30 minute LAD ligation, solution switch -10 mins. Fisher's exact test for each group vs control, \*P<0.05 (s), n=12/group. **B.** VF incidence (% of total hearts) during 30 minute LAD ligation, solution switch +10 mins. Fisher's exact test for each group vs control, \*P<0.05 (s), n=20/group.

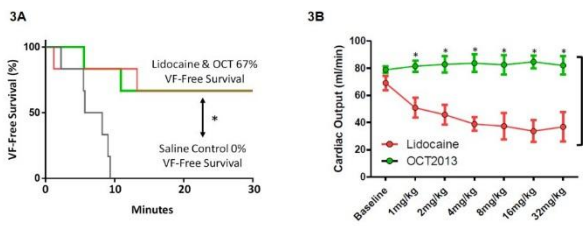


Figure 3) **A.** VF-free survival in anaesthetised rats during 30 mins LAD ligation. Chi Square test, \*P<0.05, n=6. **B.** Cardiac output in anaesthetised rats at increasing doses of OCT2013 or lidocaine. 2 way ANOVA, \*P<0.05, n=5. Values are mean ± SEM.

Conclusion: OCT2013 inhibited ischaemia-induced VF in Langendorff and *in vivo* rat models of AMI, and was as effective as lidocaine. Unlike lidocaine, however, its effects were not limited by adverse effects on cardiac output, PR interval or heart rate. Further investigation is required to define the full profile of OCT2013.

References:

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