CAN YOU TEACH AN OLD DOG NEW TRICKS? THE ANTI-MALARIAL HYDROXYCHLOROQUINE SHOWS PROMISE IN CARDIAC RATE CONTROL THROUGH ACTIONS AT THE SINO-ATRIAL NODE.

RA Capel (1), GR Mirams (2), KA Beattie (2), DJ Paterson (3), DA Terrar (1) and RAB Burton (3)

(1) Department of Pharmacology, University of Oxford, Mansfield Road, OX1 3QT

(2) Department of Computer Science, University of Oxford, Wolfson Building, OX1 3QD

(3) Department of Physiology, Anatomy and Genetics, University of Oxford, Sherrington Building, OX1 3PT

Hydroxychloroquine (HCQ) has been clinically prescribed since the early 1950s. Used as a prophylactic antimalarial and in chronic immune conditions, it has a good safety profile. Capitalising on a fortuitous clinical observation, we investigated the effects of HCQ on cardiac rate control.

Application of HCQ to spontaneously-beating mouse atrial preparations revealed a dose-dependent rate decrease ($9\pm3\%$ at $3\mu\text{M}$, $15\pm2\%$ at $10\mu\text{M}$) which did not occur in the presence of funny current ($I(f)$) inhibitor ZD7288 ($1\mu\text{M}$). $1\mu\text{M}$ HCQ significantly reduced spontaneous beating rate in isolated guinea pig sino-atrial node myocytes. Voltage clamp studies revealed a significant, dose-dependent $I(f)$ inhibition ($19\pm2\%$ at $3\mu\text{M}$, $32\pm7\%$ at $10\mu\text{M}$). Consistent with channel block, $I(f)$ inhibition reduced maximal conductance without affecting voltage of half-activation. L-type calcium and delayed rectifier potassium currents were also significantly reduced (1). We performed mathematical safety modelling using methods described in (2). Modelling results for a maximum free therapeutic concentration of $1\mu\text{M}$ indicated that the balance of potassium and calcium current inhibitions observed would not be expected to lengthen ventricular action potentials and placed HCQ in the 'low risk' category for Torsade de Pointes arrhythmia.

HCQ is capable of reducing cardiac beating rate by effects on $I(f)$. Given the excellent cardiac safety record of HCQ and safety profile modelling, it has potential as a rate-limiting agent. Further work will be required in order to assess any potential cardiac benefits of HCQ in disease populations.

(1) Capel et al. (2015) Heart Rhythm, In Press

(2) Mirams et al. (2011) Cardiovasc Res 91: 53-61