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Meeting abstract

State-dependent dissociation of HERG channel inhibitors

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Inhibition of HERG channels prolongs the ventricular action potential and correspondingly the QT-interval with the risk of *torsade de pointes* arrhythmias and sudden cardiac death. Many drugs induce stronger HERG channel inhibition when the cell membrane is depolarised frequently. The dependence of inhibition on the pulsing rate may yield different IC_{50} values at different frequencies and thus affect the quantification of HERG channel block. We compared the kinetics of HERG channel inhibition and recovery from block by 9 known blockers and several new propafenone derivatives at different frequencies. HERG channels were expressed heterologously in *Xenopus* oocytes and currents were measured with the two-electrode voltage-clamp technique. Frequency-dependent block was observed for amiodarone, cisapride, droperidol, haloperidol and the propafenone derivative GPV-0576 (group 1) whereas bepridil, domperidone, E-4031, terfenadine and propafenone (group 2) induced similar pulse-dependent block at all frequencies. With the group 1 compounds, HERG channels recovered from block in the presence of drug. No substantial recovery from block was observed with the second group of compounds. Washing out of bepridil, domperidone, E-4031 and terfenadine was substantially augmented by frequent pulsing. Our data suggest that apparently "trapped" drugs (group 2) dissociate from the open channel state whereas group 1 compounds dissociate from open and resting states.