Bradycardic and proarrhythmic properties of sinus node inhibitors. 

Sinus node inhibitors reduce the heart rate presumably by blocking the pacemaker current If in the cardiac conduction system. This pacemaker current is carried by four hyperpolarization-activated, cyclic nucleotide-gated cation (HCN) channels. We tested the potential subtype-specificity of the sinus node inhibitors cilobradine, ivabradine, and zatebradine using cloned HCN channels. All three substances blocked the slow inward current through human HCN1, HCN2, HCN3, and HCN4 channels. There was no subtype-specificity for the steady-state block, with mean IC50 values of 0.99, 2.25, and 1.96 microM for cilobradine, ivabradine, and zatebradine, respectively. Native If, recorded from mouse sinoatrial node cells, was slightly more efficiently blocked by cilobradine (IC50 value of 0.62 microM) than were the HCN currents. The block of If in sinoatrial node cells resulted in slower and dysrhythmic spontaneous action potentials. The in vivo action of these blockers was analyzed using telemetric ECG recordings in mice. Each compound reduced the heart rate dose-dependently from 600 to 200 bpm with ED50 values of 1.2, 4.7, and 1.8 mg/kg for cilobradine, ivabradine, and zatebradine, respectively. Beta-Adrenergic stimulation or forced physical activity only partly reversed this bradycardia. In addition to bradycardia, all three drugs induced increasing arrhythmia at concentrations greater than 5 mg/kg for cilobradine, greater than 10 mg/kg for ivabradine, and greater than 15 mg/kg for zatebradine.
for zatebradine, or greater than 15 mg/kg for ivabradine. This dysrhythmic heart rate is characterized by periodic fluctuations of the duration between the T and P wave, resembling a form of sick sinus syndrome in humans. Hence, all available sinus node inhibitors possess an as-yet-unrecognized proarrhythmic potential.