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MEETING ABSTRACT

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Cardiac ion channel profile of the antiepileptic drug retigabine

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Background: Retigabine was recently approved as a novel antiepileptic drug for the adjunctive treatment of partial onset seizures. At low-micromolar concentrations, the drug acts as an opener of neural K_V7 potassium channels ($K_V7.2$–7.5; *KCNQ2–5*), whereby K_V7 channels expressed in the heart ($K_V7.1$; *KCNQ1*) are not affected. Nevertheless, a slight but significant prolongation of the QT interval in the electrocardiogram has been demonstrated in a cardiac safety study in healthy subjects treated with retigabine (1,200 mg/day). In addition, cardiac arrhythmias were observed in a few subjects after retigabine application. This suggests that the drug may affect cardiac ion channels in therapeutic concentrations (free C_{max}, 1–5 µM), and may thereby represent a cardiac arrhythmia risk.
Methods: Ionic currents and action potentials were studied by the whole-cell patch-clamp technique. Cardiac ion channels were expressed in tSA201 cells and ventricular cardiomyocytes were isolated from Langendorff perfused guinea-pig hearts.
Results: In the present study, we therefore tested the effects of retigabine on human cardiac voltage-gated ion channels with major importance for electrical impulse propagation in the heart. These were $hK_V11.1$ potassium, $hNa_V1.5$ sodium, and $hCa_V1.2$ calcium channels, which, when functionally modulated by drugs, can account for undesirable cardiac adverse events. We found that retigabine significantly inhibits currents through $hK_V11.1$, $hNa_V1.5$, as well as $hCa_V1.2$ channels in concentrations ≥10 µM. In addition, retigabine at concentrations ≥10 µM shortened the action potential in guinea pig ventricular cardiomyocytes.
Discussion: We conclude that inhibition of cardiac ion channels and changes in action-potential duration occur at retigabine concentrations ≥10 µM, concentrations which are probably higher than those reached in the plasma of patients after “normal” drug application. The drug may therefore be relatively safe with respect to cardiac arrhythmia generation. However, in the case of intoxications due to retigabine overdoses, co-medication or other “second hit” factors, the drug’s inhibitory effects on channels may become relevant.
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