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Meeting abstract

Duramycin effects on voltage-gated ion channels: a QT-prolongation risk?

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Drug-induced prolongation of the QT interval has become a major safety concern during drug development. Duramycin, a peptide antibiotic, is in clinical development for the treatment of cystic fibrosis. It becomes deposited in cellular membranes where it binds to phosphatidylethanolamine. Duramycin may thereby change biophysical membrane properties and perturb ion channel function. Thus, its application possibly carries the risk to elicit a QT-prolongation. Here, we tested the effects of duramycin on currents through voltage-gated hERG potassium, sodium and calcium channels of various mammalian cell types in whole cell patch clamp studies. We found that duramycin bath concentrations between 1 nM and 0.1 μM did not generate any effects on these currents. Concentrations ≥0.3 μM, however, reduced the amplitudes of all the investigated currents. Moreover, sodium current fast inactivation kinetics was slowed in the presence of duramycin. The described effects exhibited concentration-dependency. A further rise in duramycin bath concentration (≥3.3 μM) induced a leak current consistent with pore formation. The reported effects of duramycin on ion channel function may be generated by disruption of biophysical membrane properties rather than by specific interaction with ion channel proteins. Our data suggest that, under therapeutic conditions (i.e. administration via inhalation), duramycin is unlikely to elicit a QT-prolongation.