The Antiarrhythmic Drug BRL-32872

Christoph A. Karle, Dierk Thomas, and Johann Kiehn

Department of Cardiology, Medical University Hospital Heidelberg, Heidelberg, Germany

Key words: Antiarrhythmic drugs—Arrhythmias—BRL-32872—Calcium channels — Cardiac action potential — Long QT syndrome — Potassium channels — Torsades de pointes.

ABSTRACT

BRL-32872 is a new antiarrhythmic drug with balanced class-III and class-IV actions as categorized by the Vaughan-Williams classification. BRL-32872 blocks the rapid component of the cardiac delayed rectifier potassium channel IKr (IC50 = 28 nM) and its molecular correlate HERG (“Human-ether-a-go-go related gene,” IC50 of 19.8 nM in cell lines) at low concentrations. It also inhibits the L-type calcium current (ICa) at higher concentrations (IC50 = 2.8 μM). This dual concentration-dependent profile of action at higher concentrations may possibly prevent “torsades de pointes” ventricular arrhythmias, which is a dangerous side effect of many other class-III antiarrhythmic drugs. With BRL-32872, an excessive prolongation of the action potential duration and consecutive QTc prolongation is prevented by a concentration-dependent increase of calcium channel block, resulting in the so-called “bell-shaped” profile of antiarrhythmic drug action. BRL-32872 is very effective in the treatment of ventricular arrhythmias in animal models of cardiac ischemia. In the ischemic hearts of animals the drug significantly reduced early afterdepolarization and ventricular tachycardia. The antiarrhythmic effect BRL-32872 has not yet been demonstrated in humans.