KB130015, A New Amiodarone Derivative with Multiple Effects on Cardiac Ion Channels

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ABSTRACT

KB130015 (KB015), a new drug structurally related to amiodarone, has been proposed to have antiarrhythmic properties. In contrast to amiodarone, KB015 markedly slows the kinetics of inactivation of Na+ channels by enhancing concentration-dependently (K0.5 ≈ 2 μM) a slow-inactivating ICa component (τslow ≈ 50 ms) at the expense of the normal, fast-inactivating component (τfast ≈ 2 to 3 ms). However, like amiodarone, KB015 slows the recovery from inactivation and causes a shift (K0.5 ≈ 6.9 μM) of the steady-state voltage-dependent inactivation to more negative potentials. Despite prolonging the opening of Na+ channels KB015 does not lengthen but often shortens the action potential duration (APD) in pig myocytes or in multicellular preparations. Only short APDs in mouse are markedly prolonged by KB015, which frequently induces early afterdepolarizations. KB015 has also an effect on other ion channels. It decreases the amplitude of the L-type Ca2+ current (ICa-L) without changing its time course, and it inhibits G-protein gated and ATP-gated K+ channels. Both the receptor-activated IK(ACh) (induced in atrial myocytes by either ACh, adenosine or sphingosylphosphorylcholine) and the receptor-independent (GTPγS-induced or background) IK(ACh) are concentration-dependently (K0.5 ≈ 0.6 – 0.9 μM) inhibited by KB015. IK(ATP) induced in atrial myocytes during metabolic inhibition with 2,4-dinitrophenol (DNP), is equally suppressed. However, KB015 has no effect on IK or on Ito. Consistent with the effects in K+ currents, KB015 does not depolarize the resting potential but antagonizes the APD shortening by muscarinic receptor activation or by DNP. Intracellular cell dialysis with KB015 has marginal or no effect on Na+ or K+ channels and does not prevent the effect of extracellularly applied drug, suggesting that KB015 interacts directly with channels at sites more easily accessible from the extracellular than the intracellular side of the membrane. At high concentrations KB015 exerts a positive inotropic action. It also interacts with thyroid hormone nuclear receptors. Its toxic effects remain largely unexplored, but it is well tolerated during chronic administration.