ABT-333 (DASABUVIR) PROLONGS THE ACTION POTENTIAL OF CANINE LEFT VENTRICULAR CELLS

Zsigmond Máté Kovács[1,2], Csaba Bálint Dienes[1,2], József Óvári[1,2], János Magyar[1,5], Tamás Bányász[1], Péter P. Nánási[1,3], Balázs Horváth[1,6], Norbert Szentandrássy[1,4]

[1]*Department of Physiology, Faculty of Medicine, University of Debrecen*
[2]*Doctoral School of Molecular Medicine, University of Debrecen*
[3]*Department of Dental Physiology and Pharmacology, Faculty of Dentistry, University of Debrecen*
[4]*Department of Basic Medical Sciences, Faculty of Dentistry, University of Debrecen*
[5]*Division of Sport Physiology, Department of Physiology, Faculty of Medicine, University of Debrecen*
[6]*Faculty of Pharmacy, University of Debrecen*

ABT-333 is an antiviral agent used against hepatitis C. The molecule, similarly to several IKr inhibitors, has a methanesulfonamide group. The arrhythmia inducing effect of ABT-333 has been previously reported. In clinical practice, ABT-333 produced this property when its plasma concentration was increased due to inhibition of its degrading enzyme.
Our goal was to investigate the acute effects of ABT-333 on the cells enzymatically isolated from canine heart left ventricles, which is a good electrophysiological model of the human heart.
Action potentials were recorded using a sharp microelectrode technique. We first applied ABT-333 in 1 μM for 15 min, followed by a 20 min washout. In further experiments we used increasing concentrations (1, 3, 10 and 30 μM, 5-5 min) in a cumulative manner.
1 μM ABT-333 reversibly increased AP duration with approximately 8%. When used in increasing concentrations, the drug also increased the action potential duration in a dose-dependent and reversible manner. The elongation was 7, 21, 37, and 50%, respectively. In addition, early afterdepolarizations occurred in some cells in the presence of higher ABT-333 concentrations (10 and 30 μM). ABT-333 reduced the maximal rate of the early repolarization phase of the action potential as well, but this effect was only partially reversible.
In light of our results, it is likely that the effect of ABT-333 on action potential is achieved primarily through the inhibition of potassium currents, mainly IKr. Slowing down early repolarization is likely due to the inhibition of transient outward potassium current.

Keywords: ABT-333, Dasabuvir, action-potential, canine, cardiomyocyte

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