Drugs 2000 Feb; 59 (2): 278-279
0012-6667/00/0002-0278/$25.00/0

Azimilide

A Viewpoint by Stanley Nattel

Montreal Heart Institute, University of Montreal, Montreal, Quebec, Canada

With the demonstration of the potential proarrhythmic capacity of antiarrhythmic compounds, the development of new drugs was curtailed and the focus shifted to reducing the risk of ventricular proarrhythmia.

Azimilide was initially developed based on its ability to block the slowly activating component (I_{Ks}) of the delayed rectifier K^+ current (I_K). I_K plays a prominent role in cardiac repolarisation, governing action potential duration (APD) and refractoriness. I_K inhibitors are used to prolong refractoriness (class III action), thereby suppressing re-entrant arrhythmias. Previous class III agents (other than amiodarone) have been highly selective for rapid I_K (I_{Kr}). I_{Kr} blockers increase APD most at slow rates, when proarrhythmia due to excessive repolarisation slowing [long QT syndrome (LQTS)] is most likely. I_{Ks}, with slower kinetics, was thought to accumulate and reduce APD during tachycardia. I_{Ks} inhibition was expected to increase APD selectively during tachyarrhythmias, maintaining efficacy with a reduced risk of LQTS.

Since the initial discovery of azimilide, things have become more complicated. First believed to be an I_{Ks}-specific blocker, azimilide was subsequently found to have important I_{Kr} blocking properties. The role of I_{Ks} in rate-dependent APD changes has been contested. Molecular studies of congenital LQTSs have revealed that although deficiencies of I_{Kr} can cause LQTS, so can dysfunction of I_{Ks}, alone or in combination with I_{Kr} abnormalities.

Where does this leave azimilide? The drug remains unusual in blocking I_{Ks} as well as I_{Kr} at clinically relevant concentrations. Is that good or bad? At the moment, we're not sure. Some evidence suggests that azimilide has more favourable rate-related APD-prolonging properties than pure I_{Kr} blockers. Limited clinical trials suggest efficacy comparable with presently available drugs against atrial fibrillation and flutter, with possibly less risk of LQTS. Azimilide is well tolerated and has convenient and predictable pharmacokinetics.

Azimilide's ultimate fate will depend on its performance in the phase III studies presently under way. If initial evidence for efficacy in atrial fibrillation with reduced risk of LQTS is maintained, azimilide will provide a valuable alternative for maintenance of sinus rhythm in patients with atrial fibrillation. Mortality reduction in the AzimiLide post-Infarct surVival Evaluation (ALIVE) would push azimilide to the forefront of antiarrhythmic therapy. However, experience in previous post-myocardial infarction mortality trials makes such a positive result seem unlikely. ▲