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HMR 1098: An Inhibitor of Cardiac ATP-Sensitive Potassium Channels

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ABSTRACT

Despite the recent progress in the management of cardiovascular disease in general, and cardiac arrhythmias in particular, sudden cardiac death remains both a problem for the practicing clinician and a major public health issue. Although the absolute number of sudden cardiac deaths has fallen in parallel with the reduction in overall cardiovascular mortality, the proportion of all cardiovascular deaths that are sudden and unexpected remains constant at approximately 50% (19,20).

Under ischemic conditions the K_{ATP} channels in the sarcolemmal membrane of the heart muscle cells are activated, leading to a shortening of the action potential duration and to increased extracellular K^+ concentrations. These factors are known to be arrhythmogenic and may lead to ventricular fibrillation (16). In order to prevent ischemically-determined shortening of the effective refractory period, we developed the novel sulfonylthiourea HMR 1883 and its sodium salt HMR 1098.

HMR 1883 prevents or attenuates the shortening of the ischemic myocardial action potential at concentrations that do not affect the K_{ATP} channels of other organs.

It protects animals against ischemically-determined arrhythmias without any hemodynamic consequences and without affecting the metabolic parameters. It has been shown to be particularly effective in a model of postinfarcted conscious dogs in which ventricular fibrillation was induced by a combination of exercise and myocardial ischemia.

In contrast to the conventional antiarrhythmics (class I and III agents), HMR 1883 does not affect the ECG parameters under nonischemic conditions and no proarrhythmic effects have been observed so far. Instead, HMR 1883 attenuates the ischemic changes in the ECG such as ST-segment deviations and QJ-time increases. At antifibrillatory doses it has no effect on the infarct size reduction due to ischemic myocardial preconditioning, whereas the nonselective K_{ATP} channel blocker glibenclamide completely abolishes the beneficial effect of preconditioning. This can be explained by the fact that glibenclamide inhibits mitochondrial K_{ATP} channels and HMR 1883 does not.

In the expected dosage range HMR 1098 did not have any effects in healthy volunteers. Further clinical studies have been designed to prove that the drug will reduce the incidence of sudden cardiac death in patients.