K⁺ channel opening: a new drug principle in cardiovascular medicine

Sir,—Nielsen-Kudsk JE et al recently reviewed K⁺ channel openers, addressing their clinical usefulness as vasodilatory and cardioprotective drugs.1 They elucidated electrical and mechanical aspects of these drugs and stated that two of them, pinacidil and nicorandil, had been given to thousands of patients without reports of adverse arrhythmias. They also mentioned that repolarisation abnormalities in terms of ST segment and T wave changes were a common finding in the electrocardiogram following administration of pinacidil. However, we feel there is cause for some concern regarding the potential proarrhythmic effects of these drugs, and we encourage prescribers to be more observant regarding arrhythmias in their practice.

It is known that augmentation of ATP regulated potassium current I_{KATP} by pinacidil increases dispersion of repolarisation in canine ventricular tissue enough to induce extrasystolic activity (phase 2 reentry) due to a marked abbreviation of the action potential in the epicardium. This electrical heterogeneity can be abolished by 4-aminopyridine, an inhibitor of potassium activity selective to block calcium independent transient outward current (I_{CAL}) or by a blocker of the ATP regulated potassium channels, glyburide.2 Moreover, we may also prevent development of ST segment elevation induced by pinacidil or coronary artery occlusion in dogs.3 Under conditions where the action potential is significantly abbreviated, I_{CAL} is diminished or even blocked resulting in decline of contractility function and oxygen consumption. Such electrophysiological modulation of the ventricular contraction is most likely the effect underlying the cardioprotective mechanism of K⁺ channel openers. The question is, however, whether a desired cardioprotective benefit from K⁺ channel openers could lead to arrhythmic events? Until more information is available, we would hesitate to accept that repolarisation abnormalities induced by pinacidil are benign in all patients. As we have seen with many drugs in the past, the initial experience may look very promising but extended use may later disclose serious side effects. Proarrhythmic effects have been obtained, however, when I_{KATP} and I_{CAL} blockers have been administered simultaneously to rats. Coronary flow was increased and fibrillatory activity was increased during acute myocardial ischemia.4 5

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This letter was shown to the authors, who reply as follows:

Sir,—We agree with Drs Gussak and Bjergaard that the cardiac electrophysiological effects of K⁺ channel openers is an important issue. As stated in our review, pharmacological activation of ATP sensitive K⁺ channels (IKATP) in the heart has the potential to produce both proarrhythmic and antiarrhythmic effects. Theoretically, shortening of the action potential duration (APD) in an ischemic myocardium induced by K⁺ channel openers would pre-dispose to reentry ventricular tachyarrhythmias, resulting from a reduction in the refractory period of regional myocardium. Moreover, regional differences in repolarisation and K⁺ accumulation may alter electrophysiological properties of a myocardial cell.6 7 Hence, new drugs might be useful in the treatment of long QT related arrhythmias.5 In the setting of acute myocardial ischemia, the contribution and interplay between different arrhythmia mechanisms is complex and incompletely understood. As a consequence, there are some experimental data showing proarhythmic and other antiarrhythmic effects of K⁺ channel openers depending on species, dose, and model of ischemia.5 8 The ability of K⁺ channel activators to reduce ischemic injury will lead to reduced the susceptibility to arrhythmias.

Although APD shortening followed by inhibition of Ca²⁺ influx, acceleration of myocyte contractile activity and preservation of ATP in the ischemic myocardium is an attractive theory to explain the cardioprotec-

Prophylactic replacement of Björk-Shiley convexo-concave heart valves: an easy-to-use tool to aid decision-making in individual patients

Sir,—Steyerberg et al1 presented an attractive model to facilitate decision-making in the use of Björk-Shiley convexo-concave prostheses. Based on admittedly idealised risks for surgical and non-surgical strategies, they have indicated how patients can maximise their chances of living a normal life span, that is, life expectancy if the valve prosthesis were not prone to breaking up. The example given, briefly, is of a 40 year old man who would be expected to live for 40.5 years. Maximising his odds of reaching the age of 65 should, according to the authors, direct the decision-making process. This, in my opinion, is not correct, and the step back with their admission that "Most patients are risk averse and attach more value to nearby years than to years in the distant future" is not strong enough to negate their thesis. Certainly the quality of life to be expected between the ages of 40 and 50 is greater than that to be expected between the ages of 55 and 65. More importantly, the probability of living to the age of 65 is one thing, but when you die, if you die before then, is another. In spite of almost identical

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