LETTERS TO THE EDITOR

Heart welcome letters commenting on papers published in the journal in the previous six months. Topics not related to papers published earlier in the journal may be introduced as a letter: letters reporting original data may be sent for peer review.

Presentation

Letters should be:
- not more than 600 words and six references in length
- typed in double spacing (fax copies and paper copy only)
- signed by all authors.

The letter may be a short table or a small figure. Please send a copy of your letter on disk. Full instructions to authors appear in the January 1997 issue of Heart (page 89).

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 eluded to electrical and pharmacological aspects of these drugs and stated that two of them, pinacidil and noraclid, 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 very observant regarding arrhythmias in their patients.

It is known that augmentation of ATP regulated potassium current IATP by pinacidil increases dispersion of repolarisation in canine ventricular tissue enough to induce extrasystolic activity (phase 2 return) due to a marked abbreviation of the action potential in the epicardium. This electrical heterogeneity can be abolished by 4-aminopyridine, which may also prevent development of ST segment elevation induced by pinacidil or coronary artery occlusion in dogs.2 Under conditions where the action potential is significantly abbreviated, IATP is diminished or even blocked resulting in decline of contractility function and oxygen consumption. Such electrophysiological modulation of the ventricular conduction 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. Promising effects have been obtained, however, when IATP and If blockers have been administered simultaneously to rats. Coronary flow was increased and fibrillatory activity decreased during acute myocardial ischaemia.3,4

1 Gussak JS, Bjerregaard P. Division of Cardiology, St Louis University Health Science Center, St Louis, MO 63117, USA

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

Sir,—We agree with Drs Gussak and Bjerregaard 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 ischaemic myocardium could potentially open ATP sensitive K+ channel openers would pre-dispose to reentry ventricular tachyarrhythmias, resulting from a reduction in the refractory period.5 We have observed regional differences in repolarisation and K+ accumulation. On the other hand, repolarisation by KATP channel opening is expected to inhibit arrhythmias due to triggered activity (early and delayed afterdepolarisations) and abnormal automaticity. These novel drugs might be useful in the treatment of long QT related arrhythmias.1 In the setting of acute myocardial ischaemia, the contribution and interplay between different arrhythmia mechanisms is complex and incompletely understood. As a consequence, there are some experimental data showing proarrhythmic and other antiarrhythmic effects of KATP openers depending on species, dose, and model of ischaemia.5 The ability of KATP channel activators to reduce ischaemia injury would tend to reduce the susceptibility to arrhythmias.

Although APD shortening followed by inhibition of Ca2+ influx, acceleration of cardiac contractile arrest, and preservation of ATP in the ischaemic myocardium is an attractive theory to explain the cardioprotective effects of KATP channel openers, the underlying mechanism is unsettled.1 Recent studies indicate that cardioprotection can be achieved at doses which do not reduce APD and that there is a lack of correlation between the APD shortening and cardioprotective effect of KATP openers.6 Thus, the question whether KATP channel activators in clinically relevant doses might be proarhythmogenic or antiarrhythmic in human and unresolved.6 To our knowledge, there are no clinical reports of proarrhythmic effects in patients treated with KATP openers as antihypertensive or antiangiinal agents. As with any new drug, we agree that it is wise to be observant and to report any suspected adverse effect.

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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 elective replacement 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 years. Maximising his odds of reaching the age of 65 should, according to the authors, direct the decision-making process. This is, in my opinion, not correct, and they move back step with their admission that “Most patients are risk averse and attach more value to nearly 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
expected survival to age 65 for a surgical and a non-surgical strategy, the surgical survival curve is close to a right angle, with a small sharp drop in survival periorientively, whereas the non-surgical curve will be more linear since cases of strut fracture will be evenly distributed over time. Although the two curves meet near age 65, the non-surgical curve lies above the surgical one at every point in time before then.

The estimated outcomes with and without surgery must favour surgery to a greater extent than in the presented case if surgery is to be recommended to the patient.

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

Sir,—Decision-making in Björk-Shiley convexo-concave heart valves essentially requires a weighing of short term surgical risks (mortality, morbidity, hospital admission) against cumulative long term risks of strut fracture. We tried to compare the mortality risks of "surgery" and "no surgery" on the same scale. To this aim, the life expectancy forms a suitable measure. Life expectancy is also often used in cost-effectiveness analyses, usually with a correction for the quality of life in different possible health states.1 The measure has not only been used in weighing short term against long term risks, but also in situations where treatments have an immediate benefit to the patient, such as thrombolytic therapy for acute myocardial infarction.

The interpretation of the life expectancy, is therefore an important issue for many decision analyses and cost-effectiveness analyses. Life expectancy reflects the number of years that a patient may expect to live, and is calculated as the area under the survival curve. It should not be confused with the actual outcome of the patient—for example, a survival of 1, 2, 3 ... years—not with the probability of reaching a certain age—for example, 65 years.

Survival curves for our example patient, a 40 year old male patient with a Björk-Shiley convexo-concave mitral heart valve. Top panel: basal life expectancy with or without discounting at 5% (dLE and LE). Lower panel: life expectancy with or without surgical replacement of the valve (LEsurg and LEnsurg); with or without discounting (dLE and LE).

The 4th Annual Conference of the International Society for Quality of Life Research will take place at The Vienna Academy of Postgraduate Medical Education and Research, Vienna from 5-9 November. For further information please contact the Scientific and Administrative Secretariat (tel: 43/1405 13 83 13; fax: 43/1 405 13 83 23; e-mail: medacad@via.at; homepage: http://www.via.at/medacad).

The 12th International Interdisciplinary Conference on Hypertension in Blacks will take place at the London Hilton, Park Lane, London from 20-24 July. For further information please contact Anne M Dubois at (US) tel: 001 770 516 7717; fax: 001 770 516 0180; or, Dale McFarlane at 0171 723 7228.)