Cardiovascular controversies

Potassium channel openers are likely to be proarrhythmic in the diseased human heart

Shawn C Black and Benedict R Lucchesi

The discovery of the adenosine triphosphate dependent potassium channel (KATP channel; ATP sensitive potassium channel) in cardiac myocytes has increased our understanding of pathophysiological, electrophysiological, and pharmacological processes of the heart. Experimental studies suggest that KATP channels are involved in ischaemic preconditioning and that pharmacological modulation of the KATP channel confers anti-ischaemic and antiarrhythmic effects upon the heart. On the basis of experimental in vivo and in vitro data, it is our viewpoint that opening of the cardiac KATP channel is potentially proarrhythmic in the postinfarcted myocardium. Although it is difficult to extrapolate experimental results to the human clinical condition, the laboratory data suggest caution in the application of KATP channel openers to the patient with ischaemic heart disease because of the potential of such drugs to manifest proarrhythmic effects. We here discuss the experimental and clinical results which, although limited, lead us to consider the negative consequences of KATP channel opening drugs in humans predisposed to epidemic periods of myocardial ischaemia.

The known cardiac electrophysiological effects of the KATP channel openers may limit, and possibly preclude, the clinical application of these drugs in selected patients with ischaemic heart disease. The Cardiac Arrhythmia Suppression Trial (CAST) showed that identification of effective drug therapy for preventing or reducing the incidence of sudden cardiac death in postmyocardial infarction patients remains elusive. In CAST, the class IC antiarrhythmics encainide and flecainide, which slow conduction and shorten Purkinje fibre action potential duration, increased the incidence of sudden death in postmyocardial infarction patients. Although the consequences of KATP channel modulation are controversial, it is unequivocal that KATP channel openers such as pinacidil shorten cardiac action potential duration. In addition to its effects on the myocyte, pinacidil also shortens the action potential duration of canine Purkinje fibres. The latter effect may be functionally similar to that produced by encainide and flecainide in humans. If the effect of pinacidil on canine Purkinje fibres occurs in human Purkinje fibres, the use of a drug such as pinacidil in patients with ischaemic heart disease risks a similar outcome to that shown by CAST: increased incidence of sudden death in patients with ischaemic heart disease treated with KATP channel openers. Experimental studies suggest that flecainide and pinacidil may have similar proarrhythmic mechanisms, since ventricular fibrillation induced by these agents was antagonised by the KATP channel blocker glibenclamide. Therefore, it is perhaps not unexpected that current antiarrhythmic drug development is directed towards interventions that lengthen cardiac action potential duration (class III drugs). Experimental studies of class III drugs support the logic for this approach and in postmyocardial infarction patients the class III drug amiodarone demonstrated efficacy against mortality.

Evidence derived from in vitro models of ischaemic heart disease support the tenet that KATP channel openers are proarrhythmic. Pharmacological opening of the KATP channel during low flow ischaemia, reperfusion after global or regional ischaemia, or hypoxic perfusion in isolated perfused rat or rabbit hearts increases the incidence of ventricular fibrillation. In each of the experimental conditions, the reduced oxygen availability decreases myocardial ATP content, thus making the KATP labile and susceptible to the influence of the selective KATP channel openers. Ventricular fibrillation induced by KATP channel openers can be prevented by glibenclamide, a specific KATP channel blocker. That proarrhythmic and proarrhythmic effects of KATP channel openers may be exacerbated by conditions such as myocardial ischaemia is supported by results showing markedly greater attenuation of cardiac action potential duration by cromakalim after 10 and 30 minutes of ischaemia. Under conditions of myocardial ischaemia or hypoxia (reduced cellular ATP), opening of the KATP channel in isolated hearts leads to ventricular fibrillation. The proarrhythmic potential of this class of drugs may not be apparent under non-ischaemic conditions where the normal ATP content of myocardial tissue maintains the KATP channel closed and unresponsive to the influence of channel openers. The possibility exists, therefore, that KATP channel openers, while without deleterious effects upon the normal myocardium, may become proarrhythmic in the diseased heart subject to periodic episodes of regional ischaemia.

The in vitro evidence that under ischaemic conditions KATP channel openers facilitate the development of ventricular fibrillation is supported by the results of Chi et al. Using an in vivo canine model, these investigators showed that pinacidil significantly increased the incidence of sudden cardiac death from ventricular fibrillation in postinfarcted animals which were otherwise at low risk for ischaemia induced ventricular fibrillation. Although it is not possible to draw direct parallels between experimental and clinical outcomes, it may be salient that the same in vivo experimental paradigm demonstrated the proarrhythmic action of flecainide. Whether a similar concordance exists between the Chi data and a clinical trial of KATP channel openers in postinfarction patients remains speculative. To examine further the proarrhythmic effects of KATP channel openers, it will be necessary to design studies that can account for the proarrhythmic consequences of shortening of the action potential duration in heterogeneously viable myocardium (normal and ischaemiically injured tissue).

Department of Pharmacology, University of Michigan Medical School, M6322 Medical Science Building 1, Ann Arbor, MI 48109-0626, USA: S C Black, B R Lucchesi. Correspondence to Dr Lucchesi.
It has not been determined whether $K_{ATP}$ channel openers are proarrhythmic or proarrhythmic in the diseased human heart. The limited available clinical data describe the effect of pinacidil administration upon electrocardiographic changes: T wave changes occur in 30% of patients treated with pinacidil and some patients have reported palpitations. The relationship of such changes to the proarrhythmic potential of $K_{ATP}$ channel openers in postmyocardial infarction patients or patients having signs of myocardial ischaemia while on $K_{ATP}$ channel opener therapy remains to be determined. Examination of the experimental data, however, supports the possibility that $K_{ATP}$ channel openers possess a pharmacological profile that favours the development of proarrhythmic effects in humans. Further animal experimentation, using relevant models, is justified, less we misjudge and repeat the experience of CAST.


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Albert J D’Alonzo and Gary J Grover

A TP sensitive potassium channel openers have several therapeutic targets such as smooth muscle relaxation (hypertension, asthma, and urinary incontinence) and acute ischaemic heart disease. Potassium non-rechannel openers are known to shorten action potential duration and to repolarise already depolarised myocardium. Theoretically, it can be hypothesised that the electrophysiological profile of potassium channel openers can increase or decrease arrhythmias depending on the type of arrhythmia developed. Mechanisms that contribute to the development and maintenance of ventricular tachycardia and fibrillation include: reentrant (circus, reflection or phase 2, or multiple wavefront reentry) and non-reentrant forms such as spontaneous activity (unifocal or multifocal), flow of injury current (current flow from depolarised to polarised tissue), and triggered activity (early or delayed afterdepolarisations). Predictions regarding the effects of potassium channel openers on arrhythmias in the diseased human heart may only be obtained, thus far, from animal models in which these arrhythmogenic mechanisms are developed. Reentry requires a physical substrate to be initiated (for example, myocardial ischaemia or infarction). Shortening of action potential duration has been hypothesised as a means to enhance reentry. However, animal models used for potassium channel opener studies include both reentrant and non-reentrant mechanisms. Thus, potassium channel openers have shown antiarrhythmic and proarrhythmic effects, as well as no propensity to influence arrhythmias. In vitro studies have demonstrated proarrhythmic activity for the potassium channel openers in isolated perfused heart preparations subjected to either global ischaemia or hypoxia. Unpublished results from our laboratories as well as others’ (W A Coetzee, personal communication) in isolated perfused rat hearts have shown that potassium channel openers have antiarrhythmic effects during regional ischaemia. The differences between various models of global and regional ischaemia and their importance remain to be elucidated.

The only in vivo canine studies showing that potassium channel openers have proarrhythmic activity come from de la Coussaye et al and Chi et al. In the former study pro-