Antiarrhythmic drugs: limited effectiveness and proarrhythmia

Summary of PhD thesis

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INTRODUCTION

Large clinical trials and meta-analytic studies revealed that most of the antiarrhythmic drugs are associated with proarrhythmia and do not increase long-term survival in man. Thus, better understanding of proarrhythmic events and better antiarrhythmic drugs are required.

K^+ channel blockers (Class III antiarrhythmics) prevent or terminate reentrant ventricular tachycardias and ventricular fibrillation (VF). These agents may also evoke severe arrhythmias e.g. torsade de pointes (TdP) and VF. Though most of the K^+ channel blockers do not only prevent, but can also induce arrhythmias in man, no experimental studies have been published in which both the antiarrhythmic and the proarrhythmic effect of these drugs would have been examined in the same species under well-defined *in vivo* experimental conditions.

In Carlsson's anesthetized rabbit model TdP is evoked by co-administration of a test agent with a selective α_1-adrenoceptor agonist. Although this method has long been used to examine the proarrhythmic activity of novel antiarrhythmic agents, the model is not yet characterized sufficiently for its clinical relevance. Importantly, the information on the effects of long-established drugs with clinically well-characterized proarrhythmic activity is sparse.

Of the major classes of antiarrhythmic drugs, class IV agents (calcium antagonists) can suppress ischemia-induced VF in animal models. (±)-Verapamil possesses selectivity for L-channels in ischemic versus non-ischemic myocardium, and this is determined in part by the facilitatory effect of extracellular K^+, which increases in concentration locally during acute ischemia. However, (±)-verapamil's ischemia-selectivity is inadequate since marked atrioventricular (AV) nodal effects and catastrophic hypotension occur at the doses necessary for VF suppression.

Mibefradil is a calcium antagonist that blocks both L and T-channels. Although it is known that mibefradil can suppress exercise related arrhythmias in dogs with healed myocardial infarction, it is not known whether the drug can suppress arrhythmias induced by sustained acute ischemia, whether it can do so without causing severe AV block or vasodilatation, or whether its beneficial or detrimental effects are T or L-channel-mediated.

Class I antiarrhythmic agents block Na^+ channels, and can be subdivided into Ia, Ib and Ic on the basis of their binding characteristics and selectivity for Na^+ versus K^+ channels. Despite their extensive clinical use, meta-analytic studies showed that these drugs are ineffective in the prevention of sudden cardiac death. Interestingly, the effects of Na^+ channel blockers on phase-1 ischemic VF have not been examined in isolated rat hearts. The lack of beneficial effects of Class I drugs on mortality implies that at least one of the forms of VF that contributes to sudden cardiac death in man (phase-1, phase-2 or reperfusion-induced) is

unaffected (or even exacerbated) by these drugs. If this is the case then, at the so-called human 'therapeutic' plasma concentrations, these drugs would be expected to fail to prevent phase-1 VF or reperfusion VF in isolated rat hearts.

Aims of the study

The primary goal of the K^+ channel blocker study was to examine both the antiarrhythmic and the proarrhythmic effect of newly developed K^+ channel blockers in the same species under well defined *in vivo* experimental conditions. The first set of experiments assessed the antiarrhythmic activity of almokalant and d-sotalol against reperfusion induced VF in anesthetized rabbits subjected to coronary artery occlusion and reperfusion. In order to examine the proarrhythmic profile of K^+ channel inhibitors, the effects of quinidine, amiodarone, d-sotalol and almokalant infusions were studied in anesthetized rabbits during α_1-adrenoceptor stimulation by phenylephrine.

The aim of the Ca^{2+} channel blocker study was to examine whether mibefradil can suppress ischemia and reperfusion arrhythmias in a controlled in vitro setting that allows for precise determination of concentration response relationships for actions on ventricles, the AV node, and coronary vessels. (±)-Verapamil was used as a positive control. The model chosen was the isolated perfused rat heart (Langendorff preparation). Arrhythmia data were contrasted with effects in separate groups of hearts on ventricular contractile function, varying perfusion K^+ content to determine whether mibefradil has larger or smaller putative ischemia-selective L-channel blocking activity than (±)-verapamil.

In the sodium channel study a set of experiments examined the antifibrillatory effect of representative Class Ia, Ib and Ic drugs, (quinidine, lidocaine and flecainide), each at two concentrations equivalent to the clinically relevant 'therapeutic' unbound and total plasma concentrations in isolated Langendorff perfused rat hearts. In order to detect antifibrillatory effects, the perfusion solutions contained 3 mM K^+. Additionally, experiments were performed to examine the proarrhythmic effects of the three drugs using perfusion solutions containing 5 mM K^+.

METHODS

Myocardial ischemia and reperfusion in anesthetized rabbits

The antiarrhythmic activity of K^+ channel inhibitors was tested in pentobarbitone-anesthetized rabbits. Blood pressure was measured in the carotid artery. After tracheal cannulation, left thoracotomy was performed and artificial ventilation was started with room

air. After pericardiotomy, a loop of atraumatic silk was placed around the first branch of the left circumflex coronary artery just under its origin. Both ends of the ligature were led out of the thoracic cavity through a flexible tube. Tightening the loop induced regional ischemia. Releasing the ligature allowed reperfusion. The electrocardiogram (ECG) was registered during the experiments using subcutaneous needle electrodes.

In the first set of experiments isotonic saline or almokalant (35 or 88 μg kg^{-1}) was administered intravenously right before the coronary artery occlusion. In the second set of experiments saline or d-sotalol (1 or 3 mg kg^{-1}) was administered intravenously prior to coronary artery occlusion.

After drug treatment coronary artery was occluded to achieve myocardial ischemia for 10 min. At the end of ischemia the ligature was released and 10 min of reperfusion followed.

Proarrhythmia experiments in anesthetized rabbits

The proarrhythmic effects of K^+ channel inhibitors were examined in α-chloralose anesthetized rabbits. Catheters were introduced into the carotid artery, the jugular vein and the marginal vein of the ear for recording arterial blood pressure and infusion of drugs, respectively. After tracheal cannulation, the animals were mechanically ventilated with room air as described above. Blood pressure and ECG were registered during the experiments as in the occlusion-reperfusion model.

In the first set of proarrhythmia experiments continuous i.v. phenylephrine infusion (15 μg kg^{-1} min^{-1}) was administered for 80 min. Ten min after the beginning of phenylephrine infusion, simultaneous and continuous i.v. almokalant infusion was given at the rate of 8.8 or 26 μg kg^{-1} min^{-1} for 70 min. Equivalent volume of isotonic saline was administered to the animals in the control group instead of almokalant.

In the second set of proarrhythmia experiments continuous i.v. phenylephrine infusion (15 μg kg^{-1} min^{-1}) was begun, and was continued for 85 min. Ten min after the beginning of phenylephrine infusion, increasing doses of almokalant (26, 88, 260 μg kg^{-1}), d-sotalol, quinidine, amiodarone (3, 10, 30 mg kg^{-1}) or isotonic saline were administered intravenously. Each dose was administered over a period of 5 min and there was a 20 min interval between each dose of the given antiarrhythmic.

Myocardial ischemia and reperfusion in isolated rat hearts

The antiarrhythmic activity of Na^+ and Ca^{2+} channel inhibitors was assessed in isolated perfused hearts excised from pentobarbital-anesthetized rats. Hearts were placed into

ice-cold solution containing (in mM), NaCl 118.5, $NaHCO_3$ 25.0, $MgSO_4$ 1.2, NaH_2PO_4 1.2, $CaCl_2$ 1.4, KCl 3 (or 5 where indicated) and glucose 11.1, then perfused according to Langendorff. ECG was recorded by implanting an electrode into the center of the region to become ischemic. A coronary occluder consisting of a silk suture threaded through a flexible tube was used for coronary occlusion. The suture was positioned around the left main coronary artery. Regional ischemia and reperfusion were induced by tightening the occluder and by releasing it.

In the first set of experiments of the Na^+ channel inhibitor study hearts were perfused with the lower concentrations of the drugs, i.e. quinidine 0.79 μM, lidocaine 3.88 μM, flecainide 0.74 μM or vehicle (time-matched control). In the second set of experiments hearts were perfused with the higher concentrations of the drugs, i.e. quinidine 7.90 μM, lidocaine 12.93 μM, flecainide 1.48 μM or vehicle (time-matched control). In these first two sets of experiments all perfusates contained 3 mM K^+. In the third and fourth sets of experiments again the same lower and higher drug concentrations were used, together with vehicle controls, but the perfusate contained 5 mM K^+.

In the Ca^{2+} channel inhibitor study, hearts were perfused with one of the following 11 solutions: control (vehicle), 10, 30, 100, 300 or 600 nM mibefradil or 10, 30, 100, 300 and 600 nM (±)-verapamil.

The left main coronary artery was occluded and after 30 min ischemia the occluder was released to achieve reperfusion.

Assessment of putative ischemia-selective L-channel blocking activity of Ca^{2+} antagonists

Isolated rat hearts were perfused with standard solution (see above) containing 3, 6 or 10 mM K^+, and a compliant non-elastic balloon was inflated with an added volume of 0.12 ml in the left ventricle. The hearts were exposed to 30, 100, 300 and 600 nM mibefradil or (±)-verapamil, sequentially. Diastolic pressure, developed pressure and coronary flow were recorded at predetermined intervals.

RESULTS AND DISCUSSION

Potassium channel inhibition

Almokalant and d-sotalol prevented reperfusion VF in anesthetized rabbits, though they exerted marked proarrhythmic effects during α_1-adrenoceptor stimulation in anesthetized rabbits. Almokalant and d-sotalol produced not only TdP as a malignant proarrhythmia, but

also VT (different from TdP) and VF in the proarrhythmia experiments. This high propensity of these drugs to evoke severe arrhythmias compromises their antiarrhythmic efficacy and precludes their use as antifibrillatory agents.

In our second proarrhythmia study when graded doses of K^+ channel inhibitors were applied there was no direct correlation between the occurrence of TdP and the infusion rate or the dose of d-sotalol and almokalant, since the percentage incidences of this arrhythmia were greatest after the administration of the medium doses of the drugs. This suggests that the incidence of TdP may not depend on the infusion rate or the dose of antiarrhythmics when graded doses are applied with an interval between each dose.

In our proarrhythmia experiments quinidine did not evoke TdP, though this drug was by far the most frequently reported drug associated with this arrhythmia. According to our results TdP generation may be a multifactorial process in the applied experimental model and the contributing factors may be slightly different from those in man. Thus, drugs which have different pharmacodynamic actions at high heart rates (seen in the rabbit) compared with effects at lower heart rates (seen in man), drugs which decrease blood pressure markedly or drugs, which possess α_1-adrenoceptor inhibitory effects, could elicit a false negative outcome (i.e., low proarrhythmic activity) in the rabbit model of TdP. (I., II., IV., V.)

Calcium channel inhibition

Mibefradil suppressed ischemia-induced VF in isolated rat hearts, but the drug was less potent than (±)-verapamil. Both drugs produced similar significant effects on coronary flow before ischemia, and both caused a similar degree of AV block.

In the contractility study, the negative inotropic and lusitropic effects of mibefradil were exacerbated by high K^+, but the magnitudes of the responses were less than those produced by (±)-verapamil.

The overall response profile suggests that the antiarrhythmic effect of mibefradil was mediated by the same molecular mechanism as that of (±)-verapamil, and that this mechanism was the same as that responsible for effects on contractile function. Mibefradil differed from (±)-verapamil only in terms of potency.

The effects of both drugs can be explained on the basis of L-channel blockade within the ischemic region. Neither drug is sufficiently ischemia-selective to achieve protection against VF at concentrations devoid of potentially hazardous vascular and AV nodal effects. This not only serves to explain the lack of efficacy of (±)-verapamil in preventing sudden cardiac death in man, but also excludes the possibility of mibefradil (or a pharmacologically

similar analogue) to possess better efficacy. It also appears from the Ca^{2+} channel inhibitor study that the T-channel is unlikely to represent a useful molecular target for VF suppression. (III.)

Sodium channel inhibition

Of the three representative Class I agents, only flecainide (Ic) prevented phase-1 ischemia-induced VF at the human 'therapeutic' free plasma concentration in isolated rat hearts, when 3 mM K^+ was used in the perfusate in order to allow high incidence of VF in controls. Quinidine (Ia) and lidocaine (Ib) prevented phase-1 VF only at the human 'therapeutic' total blood concentration, which is much greater than the free plasma concentration, and therefore inappropriately high in terms of clinical relevance. None of the three Class I antiarrhythmics prevented reperfusion-induced VF at the human 'therapeutic' free plasma concentration.

According to these results the ischemia-selective VF suppression by flecainide, and the ineffectiveness of clinically relevant concentrations of quinidine and lidocaine during both ischemia and reperfusion, despite electrocardiographic evidence of Na^+ channel blockade and (in the case of quinidine) K^+ channel blockade, confirms that the spectrum of antiarrhythmic activity of Class I agents in the isolated rat heart is narrow and weak at the equivalent of clinically safe 'therapeutic' concentrations.

In the proarrhythmia study none of the Class I antiarrhythmics increased the incidence of phase-1 ischemic VF (even as a trend) in isolated rat hearts, when 5 mM K^+ was used in the perfusate in order to keep the control VF incidence at a low level. Therefore, it would appear that clinical proarrhythmia seen with these drugs may not be related to exacerbation of the phase-1 ischaemia-induced VF. However, sporadic proarrhythmic events (e.g. a very early onset of ischemia-induced VF in a minority of hearts, and induction of sustained monomorphic VT) occurred.

These findings are consistent with, and may explain, the limited effectiveness of these Na^+ channel inhibitors against sudden cardiac death in man. (VI.)

THE THESIS IS BASED ON THE FOLLOWING PAPERS

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Impact factor: 2.236

III. Farkas A, Qureshi A, Curtis MJ. Inadequate ischaemia-selectivity limits the antiarrhythmic efficacy of mibefradil during regional ischaemia and reperfusion in the rat isolated perfused heart. *Br J Pharmacol* 1999; 128: 41-50.
Impact factor: 3.689

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V. Farkas A, Leprán I, Papp JGy. The proarrhythmic effects of intravenous quinidine, amiodarone, d-sotalol and almokalant in the anesthetized rabbit model of torsade de pointes. *J Cardiovasc Pharmacol.* In Press.
Impact factor: 2.396

VI. Farkas A, Curtis MJ. Limited antifibrillatory effectiveness of clinically-relevant concentrations of Class I antiarrhythmics in isolated perfused rat hearts. *J Cardiovasc Pharmacol.* In Press.
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