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Research Paper

Effects of K_{ATP} openers on the QT prolongation induced by HERG-blocking drugs in guinea-pigs

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Abstract

Objectives This work evaluated the potential usefulness of pharmacological activation of cardiac ATP-sensitive potassium channels (K_{ATP}) in the prevention of drug-induced QT prolongation in anaesthetised guinea-pigs. Prolongation of cardiac repolarisation and QT interval is an adverse effect of many drugs blocking HERG potassium channels. This alteration can be dangerously arrhythmogenic and has been associated with the development of a particular form of ventricular tachyarrhythmia known as torsade de pointes.

Methods The well-known K_{ATP} openers aprikalim, cromakalim and pinacidil were used. Moreover, three benzothiazine derivatives, which have been reported as potent activators of K_{ATP} channels, were also used.

Key findings Pharmacological activation of K_{ATP} channels caused a reduction of the QT prolongation, induced by astemizole, cisapride, quinidine and thioridazine. In contrast, the QT prolongation induced by haloperidol, sotalol and terfenadine, which are known to block HERG channels but also K_{ATP} channels, was not influenced by K_{ATP} activation. Glibenclamide and tolbutamide (non-selective blockers of K_{ATP} channels expressed both in sarcolemmal and in mitochondrial membranes) antagonised the effects of K_{ATP} openers, whereas 5-hydroxydecanoic acid (selective blocker of the mitochondrial K_{ATP} channels) failed to antagonise the effects of K_{ATP} openers, indicating that only the sarcolemmal K_{ATP} is involved in the cardioprotective activity.

Conclusions The data suggest that pharmacological K_{ATP} activation might represent an option for treatment of patients exposed to QT-prolonging drugs.

Keywords HERG channels; K_{ATP} channels; K_{ATP} openers; QT prolongation

Introduction

The electrocardiographic QT interval is conventionally considered as a parameter of the repolarisation process. Prolongation of the QT interval is caused by an enhanced duration of the action potential in ventricular myocytes, often due to a reduction of repolarising currents.

As regards iatrogenic QT prolongation, the alteration of ventricular action potential often derives from a drug-induced inhibition of the rapid component of the delayed rectifier K^+ current, encoded by the *HERG* gene (human ether-a-go-go related gene), known as the potassium HERG channel.[1,2] This is the primary pharmacodynamic mechanism of action of class III antiarrhythmic agents. However, it is also a relatively frequent (and absolutely undesirable) ancillary effect of a wide number of non-antiarrhythmic drugs that belong to various pharmacological classes. It is widely accepted that HERG blockage and consequent delayed repolarisation can be frequently, albeit not necessarily, associated with the development of the ventricular polymorphic tachyarrhythmia, known as torsade de pointes.[3–7] Actually, drug-induced torsade de pointes arrhythmia is quite a rare event in patients with a normal repolarisation reserve, but it can be dramatically facilitated when some risk factors are present.[3,4,8,9] Therefore, although the observation of a drug-induced QT prolongation cannot be considered as an infallible indicator of an incumbent torsade de pointes, it is considered as a worrying sign in patients exhibiting one or more risk factors and drug administration could be suspended. On the other hand, an effective pharmacological therapy against drug-induced QT prolongation could be a useful precautionary approach for

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patients who present risk factors but cannot suspend pharmacological treatment with drugs endowed with QT- prolonging effects.

Standard therapies against QT prolongation are directed towards the abolition of afterdepolarisation episodes and the normalisation of the repolarisation period. The afterdepolarisations can be abolished by intravenous administration of magnesium sulfate. The QT prolongation can be reduced by enhanced serum potassium levels. In cases of bradycardia, an increased heart rate is achieved by stimulation of β-adrenoceptors with isoproterenol, although this approach is contraindicated in the presence of ischaemic heart disease and congenital long QT syndrome. Occasionally, lidocaine has been also used for the treatment of torsade de pointes episodes.[10]

The clinical use of activators of ATP-sensitive potassium (K_{ATP}) channels has been reported. This pharmacological approach has been successfully used to treat torsade de pointes events that were refractory to other common therapeutic approaches.[10–15] K_{ATP} channels do not play any relevant role in the cardiac electrophysiological cycles and, under physiological conditions, they are in an inactivated state. In contrast, K_{ATP} channels play a pivotal role in the regulation of cardiac functions under conditions of metabolic impairment, such as hypoxia or ischaemia.[16] In fact, when the intracellular ATP concentration drops and ischaemic metabolites accumulate, the probability of activation of the K_{ATP} channel increases.

At least two K_{ATP} channel types coexist in myocardial cells: one is expressed in the sarcolemmal membrane (sarc-K_{ATP}) and the other is expressed in the inner membrane of the mitochondria (mito-K_{ATP}). It is generally accepted that the mito-K_{ATP} channels play a role in cardioprotection against ischaemic injury,[17,18] whereas the sarc-K_{ATP} channels principally contribute to membrane hyperpolarisation.[19]

Despite the reported clinical uses of K_{ATP} openers in long QT syndrome treatment, exhaustive experimental studies that evaluate their pharmacodynamic profile against drug-induced QT prolongation, are lacking. This work aimed to evaluate the effects of some representative K_{ATP} openers in the prevention of drug-induced QT prolongation in anaesthetised guinea-pigs.[20–24]

Materials and Methods

Drugs

Astemizole, cromakalim, glibenclamide, haloperidol, pinacidil, quinidine, sotalol, terfenadine, thioridazine and tolbutamide were purchased from Sigma (St Louis, MO, USA); Prepulsid (cisapride) was purchased from Janssen-Cilag SpA (Cologno Monzese, Italy); sodium pentobarbital was purchased from Sessa (Sesto San Giovanni, Italy). Aprikalim was a kind gift from Rhone-Poulenc Rorer (Vitry-sur-Seine, France). The benzothiazine derivatives were synthesised as described elsewhere.[25]

Haloperidol, astemizole, thioridazine (1.0 mg/ml) and quinidine (10.0 mg/ml) were dissolved in 0.9% NaCl, 10% dimethylsulfoxide (DMSO) and 1 N 1% HCl (vehicle 1). Terfenadine (1.0 mg/ml) was solubilised in 0.9% NaCl, 20% DMSO and 1 N 1% HCl (vehicle 2). Cisapride, sotalol (1.0 mg/ml) and sodium pentobarbital (50.0 mg/ml) were dissolved in bidistilled water.

Aprikalim (1.0 mg/ml) was dissolved in bidistilled water; cromakalim (2.0 mg/ml) was dissolved in 0.9% NaCl and 20% EtOH (vehicle 3); pinacidil (1.0 mg/ml) was dissolved in 0.9% NaCl and 20% DMSO (vehicle 4). BTZ 1, BTZ 2 and BTZ 3 (3.0 mg/ml) were dissolved in DMSO.

Glibenclamide (10.0 mg/ml) was dissolved in 20% PEG 400, 20% EtOH and 1 N 6% NaOH (vehicle 5); tolbutamide (25.0 mg/ml) was dissolved in 1 N NaHCO3 and 5-hydroxydecanoic acid (5-HD) (5.0 mg/ml) was dissolved in bidistilled water. Further dilutions were carried out in physiological solution. All solutions were freshly prepared before the experiments.

Experimental protocols

The experimental protocols were carried out in accordance with Italian Legislation (D.L.27/01/1992, no. 116) and with the European Council Directive 86/609 concerning animal experimentation, and were approved by the Ethical Committee of the University of Pisa.

Adult male Dunkin-Hartley guinea-pigs (500–550 g) were anaesthetised with an intraperitoneal injection of sodium pentobarbital (60 mg/kg). The animals were then tracheotomised and artificially ventilated with room air (70 strokes/min; 1 ml of room air/100 g of bodyweight). A jugular vein was cannulated for intravenous administration of drugs, vehicles or, when required, supplementary doses of anaesthetic (10 mg/kg). Four electrodes were positioned in the subcutaneous layer of the fore and hind limbs, and the ECG tracing was recorded in lead II or III on an electrocardiograph (model AO/FC) connected to a poligraph (model KV 380; Battaglia Rangoni, Casalecchio di Reno, Italy). Each animal was used for only one experiment and was killed with an overdose of sodium pentobarbital at the end of the experimental protocol.

The following four experimental protocols were designed in order to evaluate the potential effects of three well-known K_{ATP} openers (aprikalim, cromakalim and pinacidil) and of three new benzothiazine derivatives (BTZ1, BTZ2 and BTZ3, which showed a high level of potency as K_{ATP} activators in vascular smooth muscle)[25] (Figure 1), in guinea-pigs subjected to pharmacological treatment with QT-prolonging drugs. In addition, the possible involvement of the mito- and/or sarc-K_{ATP} channel was evaluated.

Torsadogenic drugs

After the equilibration time, seven well-known QT-prolonging drugs (astemizole, cisapride, haloperidol, quinidine, sotalol, terfenadine and thioridazine) were administered. The corresponding dosages were determined in previous works to achieve an almost maximal effect.[20] Thioridazine, haloperidol, astemizole, cisapride and sotalol, requiring a volume of 4–5 ml of vehicle, were intravenously infused at a dose of 10.0 mg/kg at a rate of 0.4–0.5 ml/min by a Harvard Apparatus infusion pump (model 2400-001; Harvard Apparatus, Holliston, MA, USA) to avoid any significant influence of rapid changes of volume and/or plasmatic concentration of electrolytes, while quinidine and terfenadine were injected in a bolus dose of 30.0 and 3.0 mg/kg, respectively. The ECG

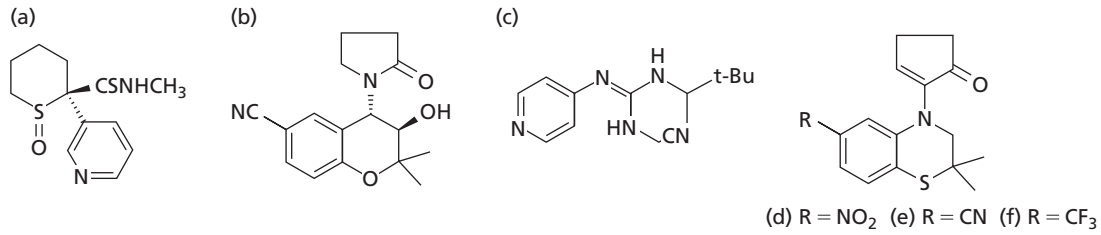

Figure 1 Chemical structures of K_{ATP} openers and benzothiazine derivatives. (a) Aprikalim. (b) Cromakalim. (c) Pinacidil. (d) BTZ 1. (e) BTZ 2. (f) BTZ 3.

tracing was analysed at 5 and 10 min and then at 10-min intervals during the experiment (1 h) following the administration of the QT-prolonging drug (Figure 2a).

K_{ATP} opener treatment

After the equilibration time, the K_{ATP} openers were administered before the QT-prolonging drug. In particular, aprikalim (1.0 mg/kg) was injected as a bolus dose 15 min before the administration of all the QT-prolonging drugs; cromakalim (1.0 mg/kg), pinacidil (3.0 mg/kg) and the new and more potent K_{ATP} openers, BTZ 1, BTZ 2 and BTZ 3 (0.1 mg/kg), were injected as bolus doses 15 min before the administration of thioridazine. The ECG tracing was analysed at 5 and 10 min and then at 10-min intervals during the experiment (1 h) following the administration of the QT-prolonging drug (Figure 2b).

K_{ATP} blocker treatment

After the equilibration time, the K_{ATP} blockers were administered before thioridazine. In particular, the non-selective K_{ATP} blocker glibenclamide (a high dose of 15.0 mg/kg was selected in order to achieve complete blockage of sarc- and mito-K_{ATP} channels) was injected as a bolus dose 20 min before the thioridazine infusion; the other non-selective K_{ATP} blocker tolbutamide (200 mg/kg) was infused by a Harvard Apparatus infusion pump at a rate of 0.4–0.5 ml/min, 40 min before thioridazine. The mito- K_{ATP} blocker 5-HD (5.0 mg/kg) was injected as a bolus dose 20 min before thioridazine. The ECG tracing was analysed at 5 and 10 min and then at 10-min intervals during the experiment (1 h) following the administration of thioridazine (Figure 2c).

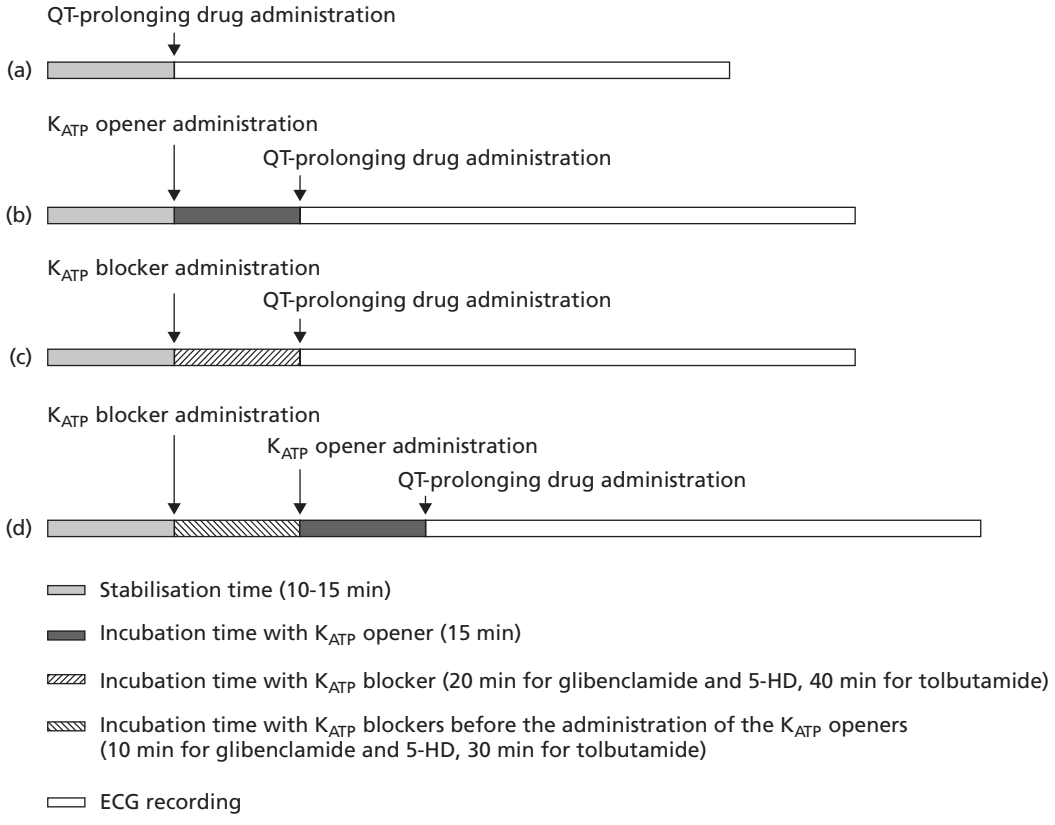

Figure 2 Schematic representation of the experimental protocols. 5-HD, 5-hydroxydecanoic acid.

Co-administration of K_{ATP} blockers and K_{ATP} openers

After the equilibration time, the K_{ATP} blocker followed by the injection of the K_{ATP} opener was administered before thioridazine. In particular, glibenclamide (15.0 mg/kg) was injected as a bolus dose 10 min before the bolus injection of aprikalim (1.0 mg/kg) or BTZ 1 (0.1 mg/kg); then, after a delay of 15 min, thioridazine was infused. Tolbutamide (200.0 mg/kg) was infused by the Harvard Apparatus infusion pump at a rate of 0.4–0.5 ml/min, 30 min before the bolus injection of aprikalim (1.0 mg/kg) or BTZ 1 (0.1 mg/kg); then, after a delay of 15 min, thioridazine was infused. The mito-K_{ATP} blocker 5-HD (5.0 mg/kg) was injected as a bolus dose 10 min before the bolus injection of K_{ATP} opener aprikalim (1.0 mg/kg); then, after a delay of 15 min, thioridazine was infused. The ECG tracing was analysed at 5 and 10 min and then at 10-min intervals during the experiment (1 h), following the administration of thioridazine (Figure 2d).

Data analysis

The maximal change of QT from the basal value, recorded at the indicated intervals, was correlated with the corresponding RR value, for the calculation of QTcB and QTcF by the Bazett[26] and Fridericia[27] algorithms ($QTcB = QT/(RR)1/2$ and $QTcF = QT/(RR)^{1/3}$, respectively). Application of the two types of algorithm (Bazett and Fridericia) yielded almost equivalent results, as previously observed.[20] The data analysis was performed with both of them in order to evaluate quali-quantitative consistency and thus to ensure a higher level of robustness for the considerations emerging from the experimental work. Previous experiments indicated that the administration of the vehicles was ineffective. Furthermore, in previous experiments, the ECG was recorded for 2.5 h in the absence of any pharmacological treatment and indicated that the basal QTc values were constantly maintained.

Statistical analysis

All data are reported as the mean ± SE. Each protocol was performed on six to eight different animals. The QTcB and QTcF values obtained with the only QT-prolonging drug were compared with the counterparts obtained after treatment with K_{ATP} openers and/or blockers, by the Student's *t*-test for unpaired data. $P \leq 0.05$ was considered significant.

Results

The recorded basal values of the ECG parameters ($RR = 288 \pm 8$; $QTcB = 394 \pm 5$; $QTcF = 320 \pm 5$) were substantially homogeneous during the four experimental protocols, indicating that the pharmacological treatments preceding the administration of the QT-prolonging drugs did not influence basal RR and QT intervals.

All the QT-prolonging drugs (astemizole, cisapride, haloperidol, quinidine, sotalol, terfenadine, thioridazine) produced a marked prolongation of the QTcB and QTcF values; the corresponding RR intervals were also lengthened (Tables 1 and 2).

Table 1 Change from baseline value of RR, QTcB and QTcF intervals after administration of QT-prolonging drugs in the presence or absence of aprikalim

Drugs	RR	QTcB	QTcF
Astemizole	126 ± 43	111 ± 11	116 ± 14
Astemizole + aprikalim	95 ± 25	49 ± 9*	58 ± 12*
Cisapride	52 ± 14	82 ± 14	73 ± 14
Cisapride + aprikalim	30 ± 6	7 ± 6**	11 ± 5**
Quinidine	119 ± 19	115 ± 22	117 ± 20
Quinidine + aprikalim	153 ± 20	47 ± 8*	65 ± 10*
Thioridazine	79 ± 16	83 ± 7	80 ± 8
Thioridazine + aprikalim	43 ± 14	42 ± 4**	39 ± 7**

Data are mean ± SEM, expressed in ms. Astemizole (10.0 mg/kg), cisapride (10.0 mg/kg), quinidine (10.0 mg/kg) and thioridazine (10.0 mg/kg) were administered intravenously in the presence or absence of aprikalim (1.0 mg/kg) to anaesthetised guinea-pigs. $*P \leq 0.05$, $**P \leq 0.01$, statistical difference between the calculated parameters and the corresponding values obtained with only the QT-prolonging drug.

Table 2 Change from baseline value of RR, QTcB and QTcF intervals after administration of QT-prolonging drugs in the presence or absence of aprikalim or BTZ 1

Drugs	RR	QTcB	QTcF
Sotalol	124 ± 34	90 ± 20	97 ± 22
Sotalol + aprikalim	150 ± 28	71 ± 12	82 ± 13
Sotalol + BTZ 1	180 ± 33	63 ± 1	81 ± 4
Haloperidol	193 ± 22	126 ± 16	146 ± 14
Haloperidol + aprikalim	221 ± 57	135 ± 25	145 ± 32
Terfenadine	107 ± 12	94 ± 4	96 ± 4
Terfenadine + aprikalim	78 ± 12	66 ± 8*	68 ± 6*
Terfenadine + BTZ 1	113 ± 18	124 ± 10	124 ± 12

Data are the mean ± SEM, expressed in ms. Sotalol (10.0 mg/kg), haloperidol (10.0 mg/kg) and terfenadine (3.0 mg/kg) were administered intravenously in the presence or absence of aprikalim (1.0 mg/kg) or BTZ 1 (0.1 mg/kg) to anaesthetised guinea-pigs. $*P \leq 0.05$, $**P \leq 0.01$, statistical difference between the calculated parameters and the corresponding values obtained with only the QT-prolonging drug.

Pretreatment with the K_{ATP} opener aprikalim (1.0 mg/kg) attenuated the prolongation of QTc values induced by astemizole, cisapride, quinidine and thioridazine (Tables 1 and 2). Aprikalim (1.0 mg/kg) showed a clear (but not significant) trend in decreasing the RR prolongation induced by the above QT-prolonging drugs (with the exception of quinidine).

The QTc prolongation induced by terfenadine was also significantly (but less markedly) reduced by aprikalim and, consistently, the RR prolongation induced by terfenadine was weakly influenced by aprikalim. Pretreatment with aprikalim did not produce any significant reduction of the RR and QTc prolongation due to sotalol and haloperidol, and a similar result was also obtained when the administration of sotalol and terfenadine was preceded by the pretreatment with BTZ 1 (0.1 mg/kg) (Table 2).

Among the QT-prolonging drugs tested, thioridazine was used to study the effects of the other K_{ATP} openers. As with aprikalim, the K_{ATP} openers cromakalim (1.0 mg/kg),

pinacidil (3.0 mg/kg), BTZ 1, BTZ 2 and BTZ 3 (0.1 mg/kg) significantly reduced the prolongation of QTc values induced by thioridazine. As observed for aprikalim, cromakalim (1.0 mg/kg), pinacidil (3.0 mg/kg), BTZ 1, BTZ 2 and BTZ 3 (0.1 mg/kg) showed a trend in decreasing the RR prolongation induced by thioridazine (Table 3).

The actions of aprikalim (1.0 mg/kg) and BTZ 1 (0.1 mg/kg) against the effect of thioridazine were antagonised by the two non-selective (acting on both sarc- and mito-K_{ATP} channels) K_{ATP} blockers, glibenclamide (15.0 mg/kg) and tolbutamide (200.0 mg/kg) (Table 4).

The mito-K_{ATP} blocker 5-HD (5.0 mg/kg) was ineffective in inhibiting the action of aprikalim (Table 4). The K_{ATP} blockers glibenclamide, tolbutamide and 5-HD did not significantly reduce the effects of thioridazine on the QTc values. Tolbutamide actually caused an increased thioridazine-induced prolongation of QTc values (Table 5).

Table 3 Change from baseline value of RR, QTcB and QTcF intervals after administration of thioridazine in the presence or absence of K_{ATP} openers

Drugs	RR	QTcB	QTcF
Thioridazine	80 ± 16	83 ± 7	80 ± 8
Thioridazine + aprikalim	43 ± 14	42 ± 4**	39 ± 7**
Thioridazine + cromakalim	41 ± 13	53 ± 10*	51 ± 10*
Thioridazine + pinacidil	52 ± 14	52 ± 9*	49 ± 8*
Thioridazine + BTZ 1	23 ± 11	21 ± 8***	21 ± 10***
Thioridazine + BTZ 2	55 ± 14	39 ± 3**	42 ± 2**
Thioridazine + BTZ 3	43 ± 21	49 ± 6*	47 ± 7*

Data are the mean ± SEM, expressed in ms. Thioridazine was administered by intravenous infusion in the presence or absence of the K_{ATP} blockers to anaesthetised guinea-pigs. *$P \leq 0.05$, **$P \leq 0.01$, statistical difference between the calculated parameters and the corresponding values obtained with thioridazine alone.

Table 4 Change from baseline value of RR, QTcB and QTcF intervals after intravenous administration of thioridazine in the presence or absence of K_{ATP} blockers and K_{ATP} opener

Drugs	RR	QTcB	QTcF
Thioridazine	80 ± 16	83 ± 7	80 ± 8
Thioridazine + glibenclamide + aprikalim	38 ± 17	62 ± 5	59 ± 8
Thioridazine + tolbutamide + aprikalim	61 ± 29	64 ± 9	64 ± 12
Thioridazine + glibenclamide + BTZ 1	38 ± 12	52 ± 8*†	50 ± 8*†
Thioridazine + tolbutamide + BTZ 1	115 ± 15	101 ± 3†††	104 ± 3†††
Thioridazine + 5-HD + aprikalim	18 ± 9	39 ± 13*	36 ± 15*

Data are the mean ± SEM, expressed in ms. Thioridazine was administered by intravenous infusion in the presence or absence of K_{ATP} blockers and K_{ATP} opener to anaesthetised guinea-pigs. *$P \leq 0.05$, **$P \leq 0.01$, statistical difference between the calculated parameters and the corresponding values obtained with thioridazine alone. $^{\dagger}P \leq 0.05$, $^{\dagger\dagger\dagger}P \leq 0.001$, statistical difference between the QTcB and QTcF values and the corresponding values obtained with thioridazine + BTZ 1.

Table 5 Change from baseline value of RR, QTcB and QTcF intervals after intravenous administration of thioridazine in the presence and in the absence of the K_{ATP} blockers

Drugs	RR	QTcB	QTcF
Thioridazine	80 ± 16	83 ± 7	80 ± 8
Thioridazine + glibenclamide	115 ± 26	101 ± 11	107 ± 12
Thioridazine + tolbutamide	119 ± 36	129 ± 25*	129 ± 26*
Thioridazine + 5-HD	110 ± 15	84 ± 11	91 ± 8

Data are the mean ± SEM, expressed in ms. Thioridazine was administered by intravenous infusion in the presence or absence of the K_{ATP} openers to anaesthetised guinea-pigs. *$P \leq 0.05$, **$P \leq 0.01$, statistical difference between the calculated parameters and the corresponding values obtained with thioridazine alone.

Discussion

As previously observed, all the torsadogenic drugs selected (astemizole, cisapride, haloperidol, quinidine, sotalol, terfenadine and thioridazine) prolonged the QTcB, QTcF and RR intervals, in anaesthetised guinea-pigs.[20,24] The K_{ATP} opener aprikalim caused a marked reduction of the prolongation of QTc values induced by four QT-prolonging drugs, astemizole, cisapride, quinidine and thioridazine. In contrast, aprikalim did not produce such an effect against the QTc prolongation induced by haloperidol and sotalol. These two drugs, well-known potassium HERG blockers, also have the ability to block the K_{ATP} channel.[28,29] Hence, it can be hypothesised that, on one hand, haloperidol and sotalol delayed the cardiac repolarisation through the blockage of the HERG channel, while they antagonised the effects of aprikalim through the blockage of K_{ATP} channels.

The terfenadine-induced QTc prolongation was weakly (albeit significantly) inhibited by aprikalim and was not significantly inhibited by BTZ 1. As with sotalol and haloperidol, terfenadine has been reported as a blocker of either HERG and K_{ATP} channels,[30] and again this feature can satisfactorily explain the experimental observations.

Thioridazine, whose interaction with HERG has been well described from a mechanistic point of view,[31] was arbitrarily selected to further investigate the effects of other K_{ATP} openers. The thioridazine-induced QTc prolongation was significantly inhibited by cromakalim and pinacidil. In accordance with the high level of potency shown by BTZ 1, BTZ 2 and BTZ 3 on vascular smooth muscle K_{ATP} channels, low doses of these benzothiazine derivatives reduced the QT-prolonging effects of thioridazine.

In order to demonstrate that the observed effects of the K_{ATP} openers were actually due to the activation of K_{ATP} channels, some K_{ATP} blockers were also used. Both glibenclamide and tolbutamide, the K_{ATP} blockers acting on both sarc- and mito-K_{ATP} channels, seemingly caused a 'potentiating' trend on the effects of thioridazine on QTc prolongation. Such an effect was particularly significant for tolbutamide. By contrast, the effects of the mito-K_{ATP} blocker 5-HD on the QT prolongation induced by thioridazine were negligible.

When glibenclamide and tolbutamide were injected before aprikalim, they antagonised the effects of the K_{ATP}

opener. Indeed, the QT prolongation induced by thioridazine under such experimental conditions (the presence of both the K_{ATP} blocker and the K_{ATP} opener) was equivalent to that induced by the administration of only thioridazine.

At the cardiac level, K_{ATP} channels are mainly known because their activation plays a key role in the endogenous mechanisms of ischaemic preconditioning. Consistently, exogenous K_{ATP} activators are able to induce a pharmacological preconditioning and to enhance the resistance of myocardiocytes against ischaemic episodes. Although the contribution of mito- and/or sarc-K_{ATP} to this phenomenon is still the object of intense debate,[32] a prevalent role of mito-K_{ATP} in reducing the cell apoptotic death following ischaemia/reperfusion is suggested by several studies;[33,34] indeed, selective openers of mito-K_{ATP} are viewed as promising anti-ischaemic drugs.[35–38] Nevertheless, there is also clear evidence about the possible contribution of sarc-K_{ATP} in reducing the ischaemia-induced injury and, in particular, the arrhythmias associated with ischaemia/reperfusion.[39–41]

Although there are clear mechanistic differences between drug-induced iatrogenic arrhythmias and arrhythmias associated with ischaemia/reperfusion, we also evaluated the possible role played by mito-K_{ATP} channels in reducing the QT-prolonging effects of thioridazine. The selective mito-K_{ATP} blocker 5-HD did not antagonise the protective effects of aprikalim on thioridazine-induced QT prolongation. Therefore, we suggest that only the opening of the sarc-K_{ATP} channel plays a dominant role in the effects exhibited by K_{ATP} openers against drug-induced QT prolongation.

Conclusions

The results of this study suggest the possible usefulness of K_{ATP} openers as a precautionary treatment for patients (exhibiting one or more risk factors) inevitably exposed to a drug with QT-prolonging properties. However, the use of such a treatment should be preceded by a careful examination of the basic pharmacodynamic profile of each QT-prolonging drug. In fact, drugs such as haloperidol, sotalol and terfenadine, which block both HERG and also K_{ATP} channels, possess an intrinsic ability to antagonise the activity of K_{ATP} openers, abolishing their possible beneficial effects.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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