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Prevention of clofilium-induced torsade de pointes by prostaglandin E_2 does not involve ATP-dependent K^+ channels

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Abstract

Drugs that prolong the QT interval can trigger the life-threatening arrhythmia, torsade de pointes, but there is a poor correlation between the extent of QT prolongation and the occurrence of torsade de pointes. The clinical status of a patient may modify the arrhythmogenicity of drugs; thus, we have investigated whether a mediator of fever and inflammation, prostaglandin E_2, alters the proarrhythmic effects of clofilium. In pentobarbitone-anaesthetized, open-chest, α-adrenoceptor-stimulated rabbits, prostaglandin E_2 0.28, 0.84 and 2.80 nmol kg^{-1} min^{-1}, infused into the left ventricle, reduced the incidence of torsade de pointes from 50% in controls to 20%, 20% and 0%, respectively ($n = 10$ per group). Pretreatment with glibenclamide (10 μmol kg^{-1}) did not alter the antiarrhythmic effect of prostaglandin E_2 (2.80 nmol kg^{-1} min^{-1}). These results indicate that prostaglandin E_2 prevents drug-induced torsade de pointes and that this action of prostaglandin E_2 is not mediated via opening of ATP-dependent K^+ channels (K_{ATP}).
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Keywords: Torsade de pointes; QT prolongation; Prostaglandin E_2; K^+ channel; ATP-dependent K^+ channel; Proarrhythmia

1. Introduction

QT prolongation and torsade de pointes are serious adverse effects of a number of drugs, including those used for non-cardiac as well as cardiac indications. Many drugs that cause the acquired long QT syndrome do so via actions on cardiac ion channels, e.g., block of current through rapidly activating delayed rectifier K^+ channels (I_{Kr}) (Viskin, 1999). However, there is a lack of correlation between the extent of QT prolongation and the occurrence of torsade de pointes (Hondeghem et al., 2001a,b; Julian et al., 1997; Mattioni et al., 1989), and it is not clear why some individuals experience drug-induced torsade de pointes while others do not. Bradycardia and hypokalemia are known to exacerbate QT prolongation (Vos et al., 2001), and it is possible that other factors that vary, e.g., as a consequence of disease pathology or severity, may influence QT prolongation and the propensity for torsade de pointes to occur.

Among the non-cardiac drugs that can cause QT prolongation and torsade de pointes are antihistamines, e.g., terfenadine (Crumb et al., 1995; Woosley et al., 1993), antibiotics, e.g., erythromycin (Daleau et al., 1995; Oberg and Bauman, 1995; Rubart et al., 1993), and antimalarial drugs, e.g., halofantrine (Batey and Coker, 2002; Monlun et al., 1993; Nosten et al., 1993). Although there are no common chemical features of these particular groups of drugs, they are all used in situations where patients may have fever or inflammatory conditions. It is well established that prostanoids, particularly those of the prostaglandin E series contribute to the development of both fever and inflammation. There is also evidence that prostaglandin E_2 has effects on K^+ channels, as it has been reported to open ATP-dependent K^+ channels (K_{ATP}) (Bouchard et al., 1994) and to reduce I_{Kr} (Ren et al., 1995). The former action would be expected to shorten cardiac action potential duration, whereas a reduction of I_{Kr} would increase action potential duration and prolong QT intervals. Thus, it is possible that prostaglandin E_2, released in the development of fever or inflammation, may influence the severity and outcome of the acquired long QT syndrome.

Clofilium is an analogue of bretylium which also has class III antiarrhythmic action via blockade of I_{Kr} (Kowey et

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al., 1985). It has been used by several groups studying the development of torsade de pointes in animal models and provides a useful positive control (Batey and Coker, 2002; Buchanan et al., 1993; Carlsson et al., 1990). The aims of the experiments described here were first, to investigate whether prostaglandin E_2 exacerbates or reduces clofilium-induced torsade de pointes and second, to determine whether actions on K_{ATP} channels were involved.

2. Materials and methods

2.1. Animals

The experiments were performed on 60 male New Zealand White rabbits (2.6–3.4 kg, Charles River, Margate, Kent, UK). The animal handling protocols were in accordance with the Guidance on the Operation on the Animals (Scientific Procedures) Act 1986, London, UK and also adhered to European Community guidelines for the use of experimental animals. Experiments were carried out under the authority of Project Licence No. 40/1702 and approved by the University of Liverpool Animal Welfare Committee.

2.2. Anaesthetized rabbit preparation

The effects of prostaglandin E_2 on clofilium-induced torsade de pointes were examined in α-adrenoceptor-stimulated, pentobarbitone-anaesthetized, open-chest rabbits using methods described in detail recently (Batey and Coker, 2002; Farkas and Coker, 2002). Briefly, 15 min after applying lignocaine ointment to a marginal ear vein, general anaesthesia was induced by intravenous administration of sodium pentobarbitone, ~ 30 mg kg^{-1}. Additional bolus doses of pentobarbitone (6 mg) were administered when necessary to maintain an adequate depth of anaesthesia. Animals were prepared for the measurement of heart rate, arterial blood pressure and simultaneous recording of the electrocardiogram (ECG) from all three limb leads. The chest was opened via a mid-line thoracotomy and an electrode placed in contact with the left ventricular epicardial surface for monophasic action potential recording. Signals were recorded via Gould amplifiers on a Po-Ne-Mah P3 data acquisition and analysis system (Farkas and Coker, 2002). Blood gases, pH and K^+ were measured at intervals throughout the experiments. After completion of the surgical preparation, there was an equilibration period of at least 20 min.

2.3. Experimental protocol

Rabbits were assigned randomly to one of four groups to receive vehicle or prostaglandin E_2 (0.28, 0.84 or 2.80 nmol kg^{-1} min^{-1}). At time zero, phenylephrine infusion was begun at 75 nmol kg^{-1} min^{-1}. After 5 min, infusions of prostaglandin E_2 and the lowest rate of clofilium (20 nmol kg^{-1} min^{-1}) were begun and administered simultaneously for 19 min. Clofilium was infused intravenously, whereas the prostaglandin E_2 was administered directly into the left ventricle via a carotid cannula in order to avoid early elimination of prostaglandin E_2 in the lungs. At 15 min, the phenylephrine infusion rate was increased to 150 nmol kg^{-1} min^{-1} with further increases to 225 and 300 nmol kg^{-1} min^{-1} at 18 and 21 min. At 24 min, all three infusions (phenylephrine, clofilium and prostaglandin E_2) were stopped and a 10-min drug-free interval followed. This cycle of drug administration was repeated twice more using the same infusion rates for phenylephrine and prostaglandin E_2 but increasing the infusion rate of clofilium to 60 then 200 nmol kg^{-1} min^{-1}. The protocol for administration of phenylephrine and clofilium has been illustrated previously (Batey and Coker, 2002; Farkas and Coker, 2002).

In order to examine whether K_{ATP} channels are involved in the effects of prostaglandin E_2, two further groups were pretreated randomly with intravenous infusions of glibenclamide (10 μmol kg^{-1}) or its vehicle. The pretreatment was administered from −10 to −5 min. At 0 min, the drug administration protocol described above was started with phenylephrine, clofilium and the highest dose of prostaglandin E_2 (2.80 nmol kg^{-1} min^{-1}).

2.4. Postexperiment analysis

Data were replayed on a personal computer for retrieval of haemodynamic parameters, arrhythmia diagnosis and measurement of ECG intervals and monophasic action potential duration. ECG intervals were measured by manual positioning of on-screen markers as described previously (Batey and Coker, 2002; Farkas and Coker, 2002). The values for QT interval were corrected for heart rate by using the formula: $QTc = QT - 0.704(RR - 250)$, which has been shown previously to be appropriate for these rabbits in our laboratory (Batey and Coker, 2002). Ventricular premature beats, bigeminy, salvos, ventricular tachycardia and ventricular fibrillation were defined in accordance with the Lambeth Conventions (Walker et al., 1988), and torsade de pointes was defined as a polymorphic ventricular tachycardia of five or more beats where clear twisting of the QRS complexes around the isoelectric line could be seen in at least one ECG lead (Batey and Coker, 2002). An example of clofilium-induced torsade de pointes is shown in Fig. 1. Blocks in the conduction system were also monitored. Conduction disturbances included atrioventricular blocks and intraventricular conduction defects (right or left bundle branch block).

2.5. Drugs

Drugs and chemicals were purchased from the following suppliers: clofilium (clofilium tosylate), glibenclamide, phenylephrine (L-phenylephrine HCl), prostaglandin E_2, polyethylene glycol 400 and ethanol from Sigma (Poole,

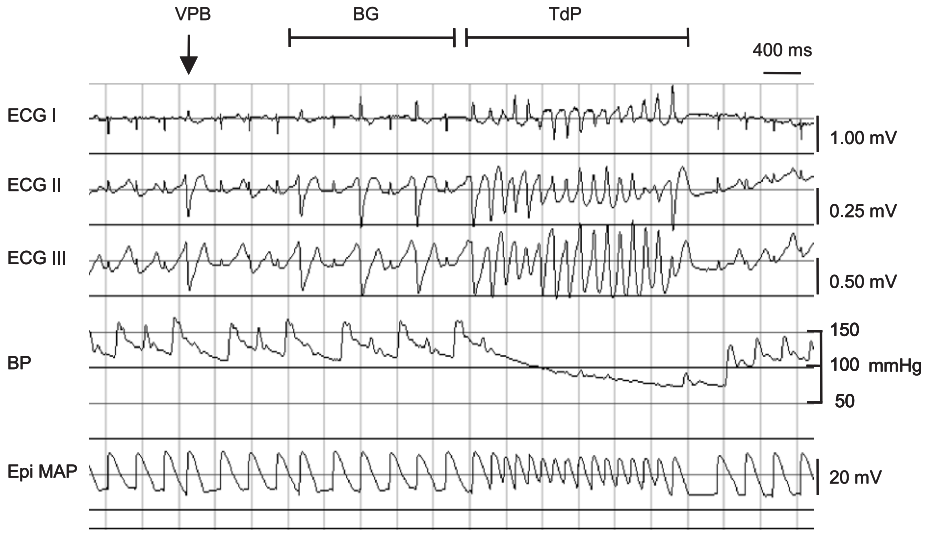

Fig. 1. An example of clofilium-induced torsade de pointes (TdP). ECG I–III, Lead I, Lead II and Lead III limb lead electrocardiograms; BP, arterial blood pressure; Epi MAP, epicardial monophasic action potential; VPB, ventricular premature beat; BG, bigeminy.

Dorset, UK), sodium pentobarbitone (Sagatal®) from National Veterinary Supplies (Stoke-on-Trent, UK) and heparin-sodium (Multiparin®) and lignocaine ointment (Lignocaine Ointment BP 5%) from the Royal Liverpool University Hospital Pharmacy Department. The drug vehicle was saline, except for prostaglandin E_2–1% ethanol in saline and glibenclamide–20% polyethylene glycol 400, 20% ethanol, 6% NaOH (I M) in distilled water.

2.6. Statistical evaluation

Data are expressed as mean ± standard error of the mean (S.E.M.). Shapiro–Wilk tests revealed that some data were not distributed normally. Kruskal–Wallis or Mann–Whitney *U* tests were used for comparisons between groups and Friedman or Wilcoxon tests for within-group comparisons. Arrhythmia incidences were compared using Fisher's exact probability test. Differences were considered statistically significant when $P < 0.05$.

3. Results

3.1. Arrhythmias

In control rabbits, clofilium caused arrhythmias ranging in severity from single ventricular premature beats to ventricular fibrillation. The incidence of ventricular premature beats, bigeminy and salvos was 100%, ventricular tachycardia was seen in 60% and ventricular fibrillation in 10% of the controls. Torsade de pointes occurred in 5 out of 10 control rabbits, with the highest incidence of torsade de pointes occurring during the second cycle of drug administration (Fig. 2). Conduction blocks were also observed in the majority of control rabbits with similar frequency in the second and third cycles of drug administration (Fig. 2). Prostaglandin E_2 dose-dependently reduced the occurrence of conduction blocks and torsade de pointes (Fig. 2). Other arrhythmias were also reduced by prostaglandin E_2 in a dose-dependent manner such that the total incidences of bigeminy, salvos and ventricular tachycardia were 30%, 20% and 0% with the highest dose of prostaglandin E_2 (2.8 nmol kg^{-1} min^{-1}). Pretreatment with glibenclamide (10 μmol kg^{-1}) or its vehicle did not reverse the antiarrhythmic effects of prostaglandin E_2 (Fig. 2).

3.2. Blood pressure and heart rate

In controls, phenylephrine increased blood pressure in a dose-dependent manner in each dosing cycle. Prostaglandin E_2 lowered mean arterial blood pressure and blunted the pressor response to phenylephrine in a dose-dependent manner (Fig. 3). Glibenclamide pretreatment did not affect baseline blood pressure, but did augment the pressor response to phenylephrine and partially reversed the hypotensive effect of prostaglandin E_2 (Fig. 3). Heart rate was reduced during drug administration in all three dosing cycles, and there was only partial recovery from bradycardia in the 10-min drug-free intervals in the control group (Fig. 4). Although there was some variation in baseline values for heart rate between the groups pretreated with glibenclamide and its vehicle, this became insignificant at a very early stage of the drug administration protocol. Neither prostaglandin E_2 nor glibenclamide altered the phenylephrine- and clofilium-induced changes in heart rate (Fig. 4).

3.3. ECG intervals and epicardial monophasic action potential duration

Clofilium and phenylephrine prolonged QTc intervals in the control group, whereas the highest dose of prostaglandin E_2 shortened QTc intervals significantly compared to con-

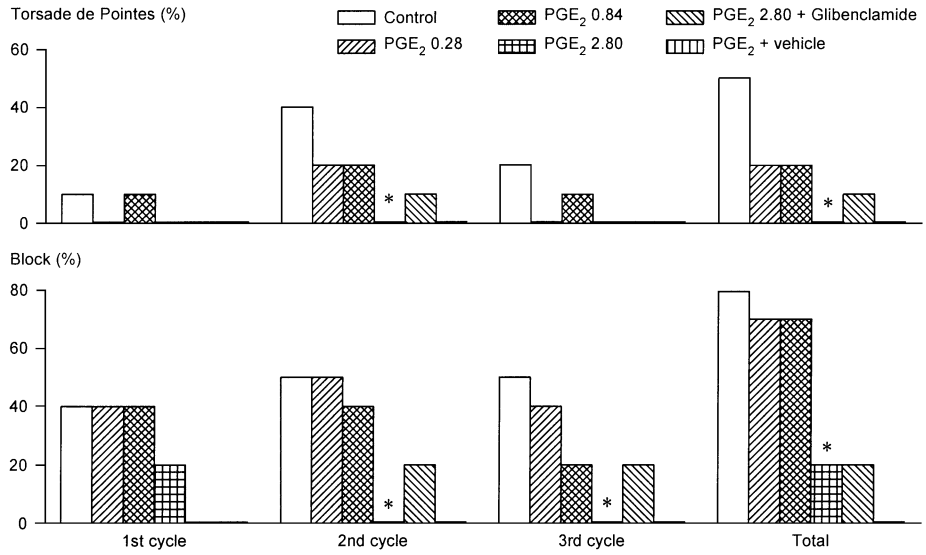

Fig. 2. Percent incidence of torsade de pointes and conduction blocks (Block) in rabbits treated with prostaglandin (PG) E_2 0.28, 0.84 or 2.80 nmol kg^{-1} min^{-1} or with glibenclamide 10 μmol kg^{-1} plus prostaglandin E_2 2.80 nmol kg^{-1} min^{-1} or the vehicle for glibenclamide plus prostaglandin E_2 2.80 nmol kg^{-1} min^{-1} during each of the three dosing cycles and the total incidence of torsade de pointes and conduction blocks throughout the whole experiment ($n = 10$ per group). *$P < 0.05$ vs. control, Fisher's exact test.

trol (Fig. 5). Glibenclamide pretreatment did not alter the baseline QTc values, but during the third cycle of phenylephrine and clofilium administration, some of the QTc intervals in the glibenclamide group were higher than those at the same time points in the vehicle-pretreated group. However, infusion of prostaglandin E_2 (2.8 nmol kg^{-1} min^{-1}) still shortened QTc intervals (Fig. 5). The epicardial monophasic action potential was also prolonged by phenylephrine and clofilium in controls, and these changes were dose-dependently attenuated by prostaglandin E_2. This effect of prostaglandin E_2 was not reversed by glibenclamide pretreatment (Fig. 6).

3.4. Blood gases and K^+

Group mean baseline P_{CO_2} values ranged from 34 ± 2 to 36 ± 1 mm Hg, while baseline P_{O_2} values ranged from 89 ± 3 to 96 ± 3 mm Hg, and there were no significant differences between groups. P_{CO_2} and P_{O_2} remained within the physiological ranges in all groups, and there were no

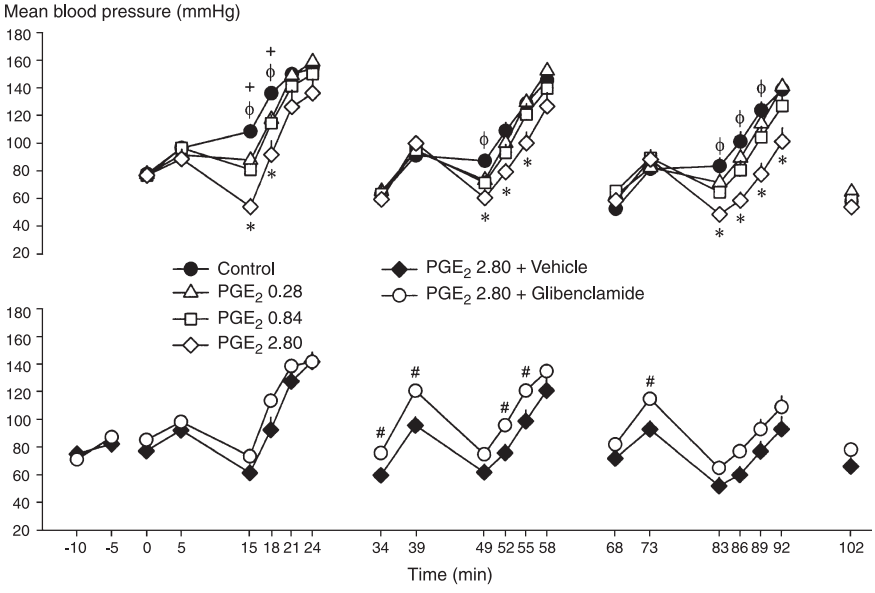

Fig. 3. Mean arterial blood pressure (BP) in rabbits treated with prostaglandin (PG) E_2 0.28, 0.84 or 2.80 nmol kg^{-1} min^{-1} or with glibenclamide 10 μmol kg^{-1} plus prostaglandin E_2 2.80 nmol kg^{-1} min^{-1} or the vehicle for glibenclamide plus prostaglandin E_2 2.80 nmol kg^{-1} min^{-1} during the three dosing cycles. Values are mean ± S.E.M. $n = 10$. *$P < 0.05$ prostaglandin E_2 2.80 nmol kg^{-1} min^{-1} vs. control; $^{\phi}P < 0.05$ prostaglandin E_2 0.84 nmol kg^{-1} min^{-1} vs. control; $^{+}P < 0.05$ prostaglandin E_2 0.28 nmol kg^{-1} min^{-1} vs. control. $^{\#}P < 0.05$ glibenclamide group vs. glibenclamide vehicle group, Kruskal–Wallis tests.

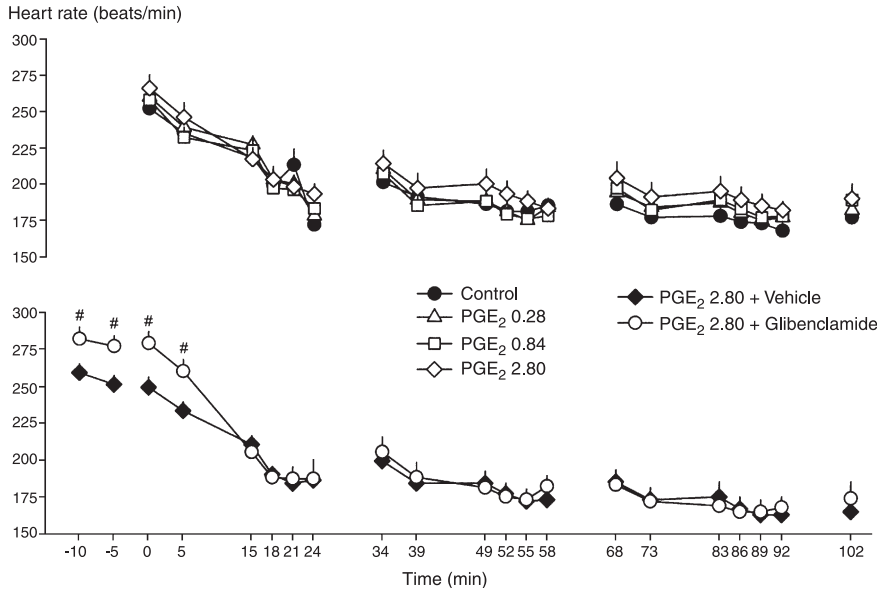

Fig. 4. Heart rate in rabbits treated with prostaglandin (PG) E_2 0.28, 0.84 or 2.80 nmol kg^{-1} min^{-1} or with glibenclamide 10 μmol kg^{-1} plus prostaglandin E_2 2.80 nmol kg^{-1} min^{-1} or the vehicle for glibenclamide plus prostaglandin E_2 2.80 nmol kg^{-1} min^{-1} during the three dosing cycles. Values are mean ± S.E.M. $n \leq 10$. At some time points towards the end of each dosing cycle, n is less than 10 because of frequent arrhythmias. $^{\#}P < 0.05$ compared to glibenclamide vehicle group, Kruskal–Wallis test.

consistent or significant prostaglandin E_2- or glibenclamide-induced changes in blood gas values during the experiments.

Pre-drug mean blood K^+ values ranged from 1.95 ± 0.20 to 2.19 ± 0.19 mM (no significant difference between groups). There was a small time-dependent increase in blood K^+ in controls from 2.06 ± 0.16 to 2.66 ± 0.14 mM by the end of the third dosing cycle, but prostaglandin E_2 treatment did not affect blood K^+ concentration during the experiment. Although the mean pre-drug blood K^+ concentrations after glibenclamide or its vehicle pretreatment (2.12 ± 0.08 and 2.04 ± 0.08 mM, respectively) were similar to those of non-pretreated groups, the blood K^+ concentrations increased in both pretreated groups to a slightly higher level than those in the non-pretreated groups by the end of the third cycle. However, the blood K^+ concentra-

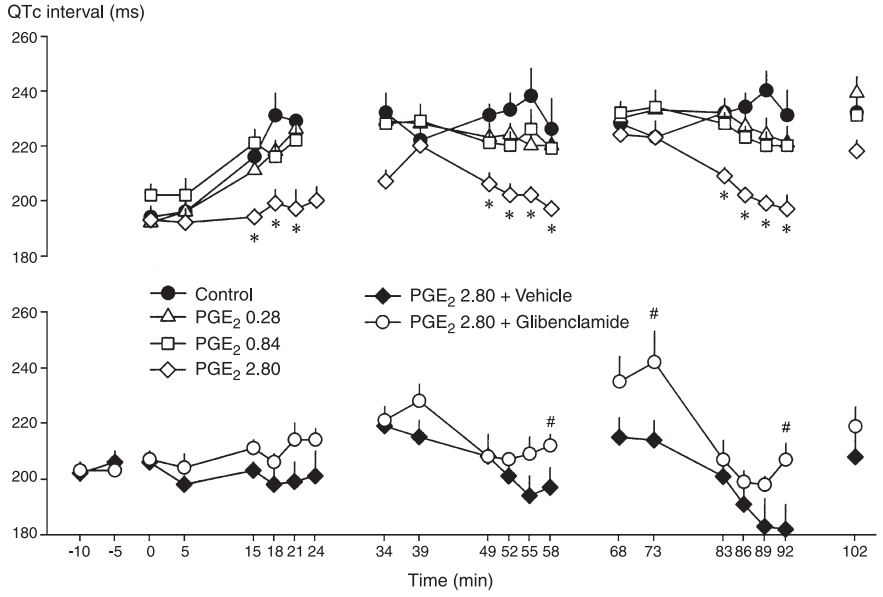

Fig. 5. Rate-corrected QT intervals (QTc) in rabbits treated with prostaglandin (PG) E_2 0.28, 0.84 or 2.80 nmol kg^{-1} min^{-1} or with glibenclamide 10 μmol kg^{-1} plus prostaglandin E_2 2.80 nmol kg^{-1} min^{-1} or the vehicle for glibenclamide plus prostaglandin E_2 2.80 nmol kg^{-1} min^{-1} during the three dosing cycles. Values are mean ± S.E.M. $n \leq 10$. At some time points towards the end of each dosing cycle, n is less than 10 because of frequent arrhythmias. $^{*}P < 0.05$ compared to controls, $^{\#}P < 0.05$ compared to glibenclamide vehicle group, Kruskal–Wallis test.

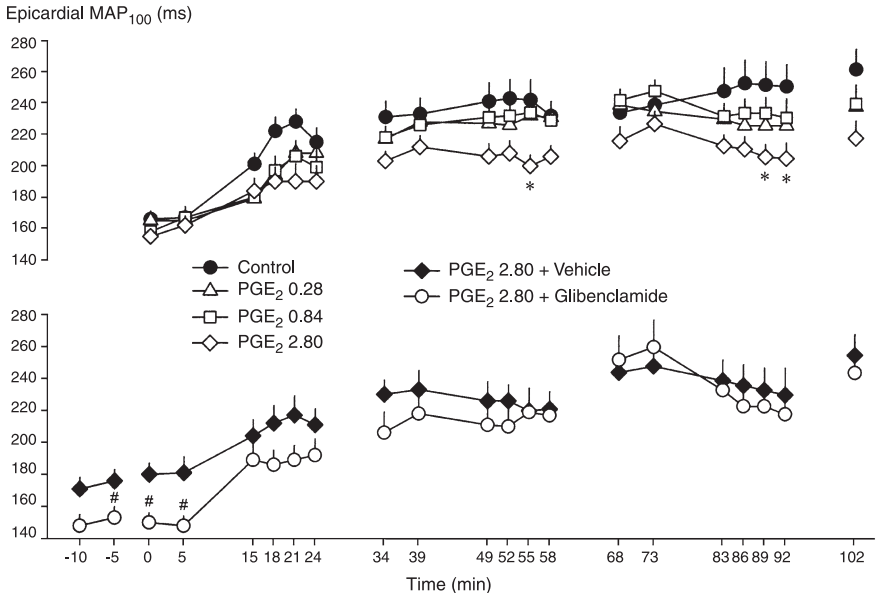

Fig. 6. Duration of epicardial monophasic action potential (MAP) measured at 100% repolarisation in rabbits treated with prostaglandin (PG) E_2 0.28, 0.84 or 2.80 nmol kg^{-1} min^{-1} or with glibenclamide 10 mmol kg^{-1} plus prostaglandin E_2 2.80 nmol kg^{-1} min^{-1} or the vehicle for glibenclamide plus prostaglandin E_2 2.80 nmol kg^{-1} min^{-1} during the three dosing cycles. Values are mean ± S.E.M. $n \leq 10$. At some time points towards the end of each dosing cycle, n is less than 10 because of frequent arrhythmias. $^{*}P<0.05$ compared to controls, $^{\#}P<0.05$ compared to glibenclamide vehicle group, Kruskal–Wallis test.

tions did not differ significantly between the glibenclamide- and its vehicle-pretreated groups at the end of the third cycle (3.50 ± 0.22 and 3.26 ± 0.23 mM, respectively) and during the whole experiments.

4. Discussion

These studies are the first to demonstrate that drug-induced torsade de pointes can be prevented by prostaglandin E_2, an endogenous mediator of fever and inflammation. They also provide evidence supporting the hypothesis that interindividual variation in susceptibility to drug-induced torsade de pointes is influenced by disease pathology or severity.

4.1. Effects of prostaglandin E_2 on blood pressure and QT intervals

As well as dose-dependently reducing torsade de pointes, prostaglandin E_2 also reduced arterial blood pressure, conduction blocks, QTc intervals and the epicardial monophasic action potential duration. It is unlikely that the depressor effect of prostaglandin E_2 contributed to the reduction in torsade de pointes as the effect of prostaglandin E_2 on blood pressure was partially reversed by glibenclamide, but the reduction of torsade de pointes was not altered. The ability of prostaglandin E_2 to lower blood pressure may involve opening of vascular K_{ATP} channels as this effect of prostaglandin E_2 was at least partially reversed by pretreatment with glibenclamide. It has been reported previously that prostaglandin E_2 activates K_{ATP} channels in the rat coronary circulation (Bouchard et al., 1994).

The highest dose of prostaglandin E_2 (2.80 nmol kg^{-1} min^{-1}) markedly attenuated the phenylephrine and clofilium-induced increases in the QTc interval. Although there were occasional time points at which the QTc interval in the glibenclamide-treated group was higher than in the vehicle-treated controls, the decrease in QTc interval when the prostaglandin E_2 was being infused during the second and third cycles of drug administration (i.e., from 39 to 58 and from 73 to 92 min, see Fig. 5) did not appear to be altered by glibenclamide. Similarly, the epicardial monophasic action potential data also suggest that glibenclamide did not alter the ability of prostaglandin E_2 to shorten cardiac repolarisation. Thus, the reductions in action potential duration and QTc intervals seen in response to prostaglandin E_2 could have contributed to the prevention of torsade de pointes. However, in control rabbits, the majority of the increase in QTc interval and action potential duration occurs during the first cycle of drug administration, whereas torsade de pointes occurs more frequently in the second cycle of drug administration. In addition, several authors have noted a lack of correlation between the extent of QTc prolongation and the occurrence of torsade de pointes (Farkas and Coker, 2002; Hondeghem et al., 2001a,b; Julian et al., 1997; Mattioni et al., 1989).

4.2. Effects of prostaglandin E_2 on arrhythmias

As well as reducing torsade de pointes, prostaglandin E_2 also reduced conduction blocks (AV block, and left and right bundle branch block), particularly during the second and third cycles of drug administration when torsade de pointes is more likely to occur. Other arrhythmias, including

bigeminy, salvos and ventricular tachycardia were also reduced by prostaglandin E_2 in the present study. Previously, prostaglandin E_2 has been reported to reduce arrhythmias induced by acute myocardial ischaemia in anaesthetized rats (Coker and Parratt, 1981). The effective dose of prostaglandin E_2 used in that previous study was 10-fold higher (10 μg kg^{-1} min^{-1} = 28 nmol kg^{-1} min^{-1}) than the highest dose used here (2.80 nmol kg^{-1} min^{-1}); however, it was given intravenously, whereas in the current study, prostaglandin E_2 was given directly into the lumen of the left ventricle to reduce clearance in the lungs. The previous study on the antiarrhythmic action of prostaglandin E_2 during ischaemia did not provide any insight into possible mechanisms underlying this action.

4.3. Lack of effect of prostaglandin E_2 on I_{Kr} or I_{KATP}

Evidence in the literature suggested that prostaglandin E_2 blocks I_{Kr} (Ren et al., 1995) but activates I_{KATP} (Bouchard et al., 1994). The results of the present experiments indicate clearly that prostaglandin E_2 reduced torsade de pointes in a dose-dependent manner, suggesting that it is unlikely to have had any significant blocking effect on I_{Kr} in these experiments. The ability of prostaglandin E_2 to reduce the QTc interval and epicardial monophasic action potential duration also supports the argument that in these experiments prostaglandin E_2 did not block I_{Kr}.

The evidence that prostaglandin E_2 opened K_{ATP} channels was obtained from studies on the rat coronary circulation (Bouchard et al., 1994). As mentioned above, in the present studies, glibenclamide partially reversed the effects of prostaglandin E_2 on blood pressure but did not alter the prostaglandin E_2-induced shortening of the QT interval or the monophasic action potential duration. These observations indicate that while prostaglandin E_2 may open vascular K_{ATP} channels, opening of cardiac myocyte K_{ATP} channels is unlikely to be involved in the shortening of the action potential duration induced by prostaglandin E_2. Since glibenclamide did cause some alteration in the vascular response to prostaglandin E_2 in the present study, this suggests that the dose used (10 μmol kg^{-1}) was high enough. This dose of glibenclamide is among the highest reported in the literature for in vivo use and has been reported previously to prevent the suppression of clofilium-induced torsade de pointes by K_{ATP} channel openers in α-adrenoceptor-stimulated anaesthetized rabbits (Carlsson et al., 1992).

4.4. Other possible mechanisms

While the experiments described above have demonstrated clearly that prostaglandin E_2 prevented torsade de pointes and that this effect was unlikely to be mediated via opening of K_{ATP} channels, they do not provide an explanation for how prostaglandin E_2 abolished torsade de pointes. The ability of prostaglandin E_2 to reduce the phenylephrine/clofilium-induced prolongation of the QTc interval and action potential duration suggests that either prostaglandin E_2 prevents a specific action of phenylephrine or clofilium that contributes to these effects, or prostaglandin E_2 has an action that physiologically antagonizes those of the proarrhythmic drug protocol.

At present, it is not clear exactly how drugs like clofilium cause torsade de pointes in α-adrenoceptor-stimulated anaesthetized rabbits. Although several drugs that can cause torsade de pointes are selective blockers of I_{Kr}, clofilium can block I_{Ks} and I_{to} as well as I_{Kr} (Castle, 1991; Li et al., 1996a, 2001). In anaesthetized rabbits an α-adrenoceptor agonist is necessary to reveal the proarrhythmic actions of drugs like clofilium (Batey and Coker, 2002; Carlsson et al., 1990). Carlsson et al. (1990) showed that prazosin prevented the proarrhythmic effects of clofilium in α-agonist-stimulated rabbits, indicating that stimulation of α-adrenoceptors is essential. As far as we are aware, prostaglandin E_2 does not block α-adrenoceptors. As well as the effects on I_{Kr} and I_{KATP} mentioned above, prostaglandin E_2 can open a Ca^{2+} activated K^+ channel in erythrocytes (Li et al., 1996b) and decrease the open probability of an inward rectifier K^+ channel in colonic epithelium (Li and Halm, 2002). Thus, it is possible that prostaglandin E_2 may open a K^+ channel in cardiac myocytes, which could explain how it shortened cardiac action potential duration. Recently, we have reported that prostaglandin E_2 shortens the effective refractory period in isolated rat cardiac muscle preparations and that this effect was likely to have been mediated via opening of inward rectifier K^+ channels (Coker and Panagopoulos, 2002). However, confirmation that prostaglandin E_2 increases I_{K1} in rabbit ventricular myocytes is necessary before this could be suggested as a mechanism to explain how prostaglandin E_2 reduced torsade de pointes in the present study.

4.5. Clinical relevance of the data

The results of these in vivo experiments have established the principle that factors that may be altered in disease, such as the release of prostaglandin E_2 during fever or inflammation, can modify the proarrhythmic activity of drugs that prolong the QT interval. As far as the clinical use of antibiotics, antihistamines and antimalarials is concerned, the evidence that prostaglandin E_2 prevents torsade de pointes suggests that the use of these drugs may be safer in severely ill patients than in those with milder disease or those who are taking a drug for prophylaxis rather than treatment.

5. Conclusions

These studies have demonstrated clearly that a mediator of inflammation and fever, prostaglandin E_2, can prevent drug-induced torsade de pointes in an anaesthetized rabbit model, indicating that disease pathology or severity can modulate drug-induced proarrhythmia. Prostaglandin E_2 also shortened

QTc intervals and epicardial monophasic action potential duration in vivo. The lack of ability of glibenclamide to prevent the effects of prostaglandin E_2 on cardiac repolarisation in vivo indicates that prostaglandin E_2 does not prevent torsade de pointes by opening K_{ATP} channels.

Acknowledgements

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References

Batey, A.J., Coker, S.J., 2002. Proarrhythmic potential of halofantrine, terfenadine and clofilium in a modified in vivo model of torsade de pointes. Br. J. Pharmacol. 135, 1003–1012.

Bouchard, J.F., Dumont, E., Lamontagne, D., 1994. Evidence that prostaglandins I_2, E_2, and D_2 may activate ATP sensitive potassium channels in the isolated rat heart. Cardiovasc. Res. 28, 901–905.

Buchanan, L.V., Kabell, G., Brunden, M.N., Gibson, J.K., 1993. Comparative assessment of ibutilide, D-sotalol, clofilium, E-4031, and UK-68,798 in a rabbit model of proarrhythmia. J. Cardiovasc. Pharmacol. 22, 540–549.

Carlsson, L., Almgren, O., Duker, G., 1990. QTU-prolongation and torsades de pointes induced by putative class III antiarrhythmic agents in the rabbit: etiology and interventions. J. Cardiovasc. Pharmacol. 16, 276–285.

Carlsson, L., Abrahamsson, C., Drews, L., Duker, G., 1992. Antiarrhythmic effects of potassium channel openers in rhythm abnormalities related to delayed repolarization. Circulation 85, 1491–1500.

Castle, N.A., 1991. Selective inhibition of potassium currents in rat ventricle by clofilium and its tertiary homolog. J. Pharmacol. Exp. Ther. 257, 342–350.

Coker, S.J., Panagopoulos, P., 2002. Evidence that prostaglandin E_2 opens cardiac inward rectifier potassium channels: an explanation for prevention of torsade de pointes. Br. J. Pharmacol. 137, 22P.

Coker, S.J., Parratt, J.R., 1981. The effects of prostaglandins E_2, $F_{2\alpha}$, prostacyclin, flurbiprofen and aspirin on arrhythmias resulting from coronary artery ligation in anaesthetized rats. Br. J. Pharmacol. 74, 155–159.

Crumb, W.J., Wible, B., Arnold, D.J., Payne, J.P., Brown, A.M., 1995. Blockade of multiple human cardiac potassium currents by the antihistamine terfenadine-possible mechanism for terfenadine-associated cardiotoxicity. Mol. Pharmacol. 47, 181–190.

Daleau, P., Lessard, E., Groleau, M.F., Turgeon, J., 1995. Erythromycin blocks the rapid component of the delayed rectifier potassium current and lengthens repolarization of guinea pig ventricular myocytes. Circulation 91, 3010–3016.

Farkas, A., Coker, S.J., 2002. Limited induction of torsade de pointes by terikalant and erythromycin in an in vivo model. Eur. J. Pharmacol. 449, 143–153.

Hondeghem, L.M., Carlsson, L., Duker, G., 2001a. Instability and triangulation of the action potential predict serious proarrhythmia, but action potential duration prolongation is antiarrhythmic. Circulation 103, 2004–2013.

Hondeghem, L.M., Dujardin, K., De Clerck, F., 2001b. Phase 2 prolongation, in the absence of instability and triangulation, antagonizes class III proarrhythmia. Cardiovasc. Res. 50, 345–353.

Julian, D.G., Camm, A.J., Frangin, G., Janse, M.J., Munoz, A., Schwartz, P.J., Simon, P., 1997. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. Lancet 349, 667–674.

Kowey, P.R., Friehling, T.D., O'Connor, K.M., Wetstein, L., Kelliher, G.J., 1985. The effect of bretylium and clofilium on dispersion of refractoriness and vulnerability to ventricular fibrillation in the ischemic feline heart. Am. Heart J. 110, 363–370.

Li, Y., Halm, D.R., 2002. Secretory modulation of basolateral membrane inwardly rectified K^+ channel in guinea pig distal colonic crypts. Am. J. Physiol. Cell Physiol. 282, C719–C735.

Li, Q., Himmel, H.M., Ravens, U., 1996a. Selectivity of class-III antiarrhythmic action of clofilium in guinea pig ventricular myocytes. J. Cardiovasc. Pharmacol. 27, 401–410.

Li, Q., Jungmann, V., Kiyatkin, A., Low, P.S., 1996b. Prostaglandin E_2 stimulates a Ca^{2+}-dependent K^+ channel in human erythrocytes and alters cell volume and filterability. J. Biol. Chem. 271, 18651–18656.

Li, R.A., Miake, J., Hoppe, U.C., Johns, D.C., Marban, E., Nuss, H.B., 2001. Functional consequences of the arrhythmogenic G306R KvLQT1 K^+ channel mutant probed by viral gene transfer in cardiomyocytes. J. Physiol. (London) 533, 127–133.

Mattioni, T.A., Zheutlin, T.A., Sarmiento, J.J., Parker, M., Lesch, M., Kehoe, R.F., 1989. Amiodarone in patients with previous drug-mediated torsade de pointes. Long-term safety and efficacy. Ann. Intern. Med. 111, 574–580.

Monlun, E., Pillet, O., Cochard, J.F., Garrigues, J.C.F., Lebras, M., 1993. Prolonged QT interval with halofantrine. Lancet 341, 1541–1542.

Nosten, F., Terkuile, F.O., Luxemburger, C., Woodrow, C., Kyle, D.E., Chongsuphajaisiddhi, T., White, N.J., 1993. Cardiac effects of antimalarial treatment with halofantrine. Lancet 341, 1054–1056.

Oberg, K.C., Bauman, J.L., 1995. QT interval prolongation and torsades de pointes due to erythromycin lactobionate. Pharmacotherapy 15, 687–692.

Ren, J., Karpinski, E., Benishin, C.G., 1995. Prostaglandin E_2 contracts vascular smooth muscle and inhibits potassium currents in vascular smooth muscle cells of rat tail artery. J. Pharmacol. Exp. Ther. 275, 710–719.

Rubart, M., Pressler, M.L., Pride, H.P., Zipes, D.P., 1993. Electrophysiological mechanisms in a canine model of erythromycin-associated long QT syndrome. Circulation 88, 1832–1844.

Viskin, S., 1999. Long QT syndromes and torsade de pointes. Lancet 354, 1625–1633.

Vos, M.A., van Opstal, J.M., Leunissen, J.D., Verduyn, S.C., 2001. Electrophysiologic parameters and predisposing factors in the generation of drug-induced torsade de pointes arrhythmias. Pharmacol. Ther. 92, 109–122.

Walker, M.J.A., Curtis, M.J., Hearse, D.J., Campbell, R.W.F., Janse, M.J., Yellon, D.M., Cobbe, S.M., Coker, S.J., Harness, J.B., Harron, D.W.G., Higgins, A.J., Julian, D.G., Lab, M.J., Manning, A.S., Northover, B.J., Parratt, J.R., Riemersma, R.A., Riva, E., Russell, D.C., Sheridan, D.J., Winslow, E., Woodward, B., 1988. The Lambeth Conventions—Guidelines for the study of arrhythmias in ischemia, infarction, and reperfusion. Cardiovasc. Res. 22, 447–455.

Woosley, R.L., Chen, Y., Freiman, J.P., Gillis, R.A., 1993. Mechanism of the cardiotoxic actions of terfenadine. JAMA 269, 1532–1536.