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K201, a multi-channel blocker, inhibits clofilium-induced torsades de pointes and attenuates an increase in repolarization

Hisashi Hasumi [a], Ryuko Matsuda [a], Ken Shimamoto [b], Yoshihito Hata [a], Noboru Kaneko [a,*]

[a] Department of Cardiology and Pneumology, Dokkyo Medical University School of Medicine 880 Kitakobayashi, Mibu, Tochigi, Japan
[b] Department of Cardiology, Tokyo Women's Medical University, Aoyama Hospital, Tokyo, Japan

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Abstract

K201 (JTV519) is a 1,4-benzothiazepine derivative that exhibits a strong cardioprotective action and acts as a multiple-channel blocker, including as a K^+ channel blocker. An experimental model of prolongation of the QT interval and torsades de pointes can be induced in rabbits by treatment with clofilium in the presence of the α_1-adrenoreceptor agonist methoxamine. In this study we examined the effects of K201 with and without methoxamine on the QT and QTc intervals, and determined whether K201 inhibits clofilium-induced torsades de pointes in the presence of methoxamine (15 μg/kg/min) in rabbits ($n=74$). Administration of K201 (0, 40, 100, 200 and 400 μg/kg/min) with and without methoxamine prolonged the QT interval in a dose-dependent manner, and torsades de pointes did not occur in any animals. However, clofilium (50 μg/kg/min) with methoxamine induced torsades de pointes in all animals (6/6). Torsades de pointes occurred at rates of 100%, 67%, 40% and 0% at K201 concentrations of 0, 50, 200 and 400 μg/kg/min, respectively, in the clofilium-infused torsades de pointes model. Therefore, 400 μg/kg/min of K201 completely inhibited clofilium-induced torsades de pointes and attenuated the increase of repolarization caused by clofilium; the inhibitory effects of K201 may be related to its pharmacological properties as an α_1-adrenoceptor blocker. Overall, our results show that K201 causes prolongation of the QT and QTc intervals, but does not induce torsades de pointes, with and without α_1-adrenoceptor stimulation. Furthermore, K201 inhibits clofilium-induced torsades de pointes, despite QT prolongation, suggesting that QT prolongation alone is not a proarrhythmic signal.

Keywords: K201 (JTV-519); Multi-channel blocker; Clofilium; α_1-Adrenoceptor blocker; QT interval prolongation; Torsades de pointes

1. Introduction

K201[1] (JTV-519), 4-[3-(4-benzylpiperidin-1-yl}propionyl)-7-methoxy-2,3,4,5-tetrahydro-1,4-benzothiazepine monohydrochloride, was originally discovered as an agent for prevention of sudden cardiac death and myocardial infarction (Kaneko, 1994). K201 has several effects, including α_1-adrenergic blocking activity, an intracellular Ca^{2+} blocking action (Kaneko, 1994), and strong cardioprotective effects against ischemia-reperfusion-induced myocardial injury (Inagaki et al., 2000; Ito et al., 2000; Kawabata et al., 2000). K201 also exhibits multi-channel blocking effects: inhibition of the fast sodium current (I_{Na}) and L-type calcium current ($I_{Ca,L}$), and blocking of the delayed rectifier potassium current (I_K) have been shown in atrial and ventricular cardiomyocytes from rabbits, rats and guinea pigs (Kimura et al., 1999; Kiriyama et al., 2000; Nakaya et al., 2000). K201 is also effective for prevention of atrial fibrillation (Kumagai et al., 2003).

Class I and III antiarrhythmic agents and non-cardiac drugs are well known to prolong the QT interval and induce torsades de pointes (Thibault and Nattel, 1999; Bednar et al., 2001; De Ponti et al., 2002; Haddad and Anderson, 2002; Roden, 2004). Amiodarone and bepridil are antiarrhythmic agents that have complex multi-channel blocking effects (Hollingshead et al., 1992; Nobe et al., 1993; Singh, 1996; Antzelevitch, 2004); these agents induce torsades de pointes and are known to cause lengthening of the action potential duration. Prolongation of the

* Corresponding author. Tel.: +81 282 86 5692; fax: +81 282 86 5643 880.
E-mail address: nkaneko@dokkyomed.ac.jp (N. Kaneko).
[1] We note that in this paper we referred to the agent using its original name, K201, rather than its alternative name, JTV519.

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QT interval is sometimes, but not always, associated with the occurrence of torsades de pointes and ventricular fibrillation (Zipes and Wellens, 1998; Straus et al., 2006). An experimental model of torsades de pointes can be prepared using a relatively low dose of the class III antiarrhythmic agent, clofilium, together with the α_1-adrenoreceptor agonist, methoxamine, and marked prolongation of the QT interval and torsades de pointes has been demonstrated in chloralose-anaesthetized rabbits (Carlsson et al., 1990). However, recent studies have shown that prolongation of the QT interval is not the sole determinant of the potential of a drug to cause torsades de pointes (Antzelevitch, 2004).

In this study, we investigated the effects of K201 with and without α_1-adrenoreceptor stimulation on QT and corrected QT (QTc) intervals, and determined whether K201 decreases or increases torsades de pointes, and attenuates or accelerates prolongation of the QT interval in a clofilium-induced torsades de pointes model in rabbits.

2. Materials and methods

2.1. Animal preparation

Seventy-four male New Zealand white rabbits (2.5 to 3.5 kg) were used in the study. The animals were allowed free access to standard feed and water, and the experiments were performed in accordance with the guidelines for animal experimentation established by the ethics committee of Dokkyo Medical University School of Medicine and Environmental Biological Life Sciences. Anesthesia was induced using thiopental sodium (20 mg/kg, one bolus administration) followed by α-chloralose (90 mg/kg/20 min, 15 mg/ml) via a marginal ear vein, and after tracheotomy the animals were artificially ventilated with room air using a ventilator (SN-480-7; Shinano, Japan). Tidal volume (10 ml/kg) and respiratory rate (30 strokes/min) were adjusted to maintain blood gases and pH within their normal physiological ranges. A double-lumen catheter was inserted into the right femoral vein for administration of each drug, and a 5Fr Millar catheter (MPC-500, Millar Instruments Inc.) was placed in the right carotid artery for recording blood pressure. Needle electrodes were applied to the surface of the limbs for recording the standard surface electrocardiogram (ECG), and lead II was used to measure ECG parameters. All experiments were conducted after an equilibration period of 10 min, and ECG parameters were measured from at least five complexes in lead II. When

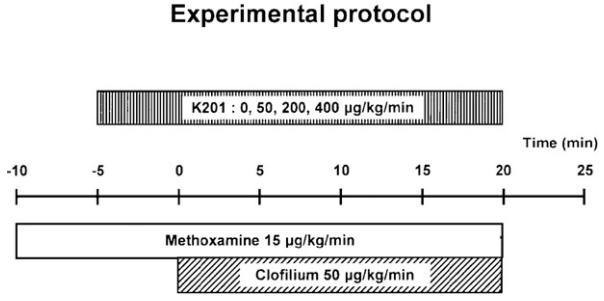

Fig. 1. Effects of K201 with infusion of clofilium and methoxamine.

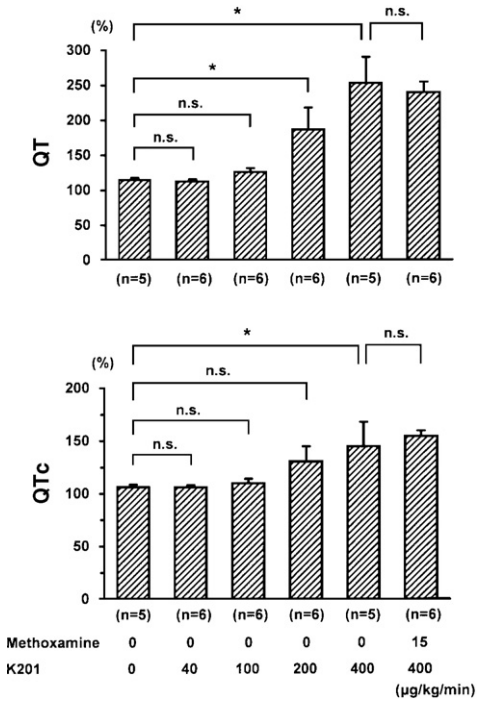

Fig. 2. Effects of K201 on QT and QTc intervals in the presence and absence of methoxamine. K201 prolonged the QT and QTc intervals dose-dependently, and prolongation of these intervals with 400 μg/kg/min K201 was similar with and without α_1-adrenoceptor stimulation. *;$P<0.05$, n.s.; not significant.

there was an interruption of a T wave with a U wave, the QT interval was measured to the end of the U wave, as described previously (Lu et al., 2000).

2.2. Experimental protocol

2.2.1. Effects of K201 on QT and QTc intervals in the presence and absence of methoxamine

In animals receiving K201 without α_1-adrenoceptor stimulation, continuous infusion of saline (infusion rate: 0.1 ml/kg/min) was started 10 min prior to administration of K201. Subsequently, K201 at a concentration of 0 ($n=5$), 40 ($n=6$), 100 ($n=6$), 200 ($n=6$) and 400 μg/kg/min ($n=5$) was administered for 30 min. In animals that received K201 with an α_1-adrenoceptor agonist (methoxamine, 15 μg/kg/min; infusion rate: 0.1 ml/kg/min), infusion of methoxamine was started 10 min prior to administration of K201; subsequently K201 (400 μg/kg/min) and methoxamine were infused for 30 min ($n=6$).

2.2.2. Effects of K201 and clofilium on hemodynamic and ECG parameters in the presence of methoxamine

Continuous infusion of methoxamine (15 μg/kg/min; infusion rate: 0.1 ml/kg/min) was started 10 min prior to administration of clofilium. Subsequently, clofilium (50 μg/kg/min) and methoxamine were infused for 20 min, although continued infusion of clofilium with methoxamine over 20 min was difficult because of occurrence of torsades de pointes, ventricular fibrillation and/or cardiac death. Analysis of the effect of K201 (400 μg/kg/min) with methoxamine (15 μg/kg/min) was

performed in the group treated using the experimental protocol described in Section 2.2.1. Clofilium and methoxamine were dissolved in saline and K201 was dissolved in 5% mannitol adjusted to pH 3.5 with 0.2% citric acid. The respective control groups received infusion of solvent only. Blood pressure and ECG were recorded simultaneously and blood pressure, heart rate, PQ, QRS, QT and QTc intervals were observed for 30 min. The parameters are shown as % changes from values (100%) measured before administration of K201 or clofilium.

2.2.3. Effects of K201 on QT and QTc intervals and clofilium-induced torsades de pointes in the presence of methoxamine

The effect of K201 was studied using the protocol shown in Fig. 1. Methoxamine (15 μg/kg/min) was infused 10 min prior to clofilium administration and then for a further 20 min concurrent with clofilium (50 μg/kg/min) infusion. K201 (0, 50 and 400 μg/kg/min, $n=6$ in each group) was infused 5 min prior to clofilium administration and then for a further 20 min. K201 at a concentration of 200 μg/kg/min was simultaneously infused with clofilium for 20 min ($n=5$). In all experiments, recordings were performed for 30 min after the start of infusion of K201.

2.3. Agents

Thiopental sodium, α-chloralose, and methoxamine were dissolved in saline and prepared at concentrations of 25, 15 and 0.15 mg/ml, respectively. Clofilium tosylate (St. Louis, MO, USA) was dissolved in saline at 0.5 mg/ml for administration at a rate of 50 μg/kg/min. K201 (provided by one of authors, N. Kaneko, who first discovered K201) was dissolved in 5% mannitol adjusted to pH 3.5 with 0.2% citric acid, and prepared at 0.5, 1, 2 and 4 mg/ml for administration at 50, 100, 200 and 400 μg/kg/min, respectively.

2.4. Data acquisition and statistical analysis

A polygraph (GE Marquette Medical Systems, Japan) was connected via a computer to a data analysis system (MP100WS

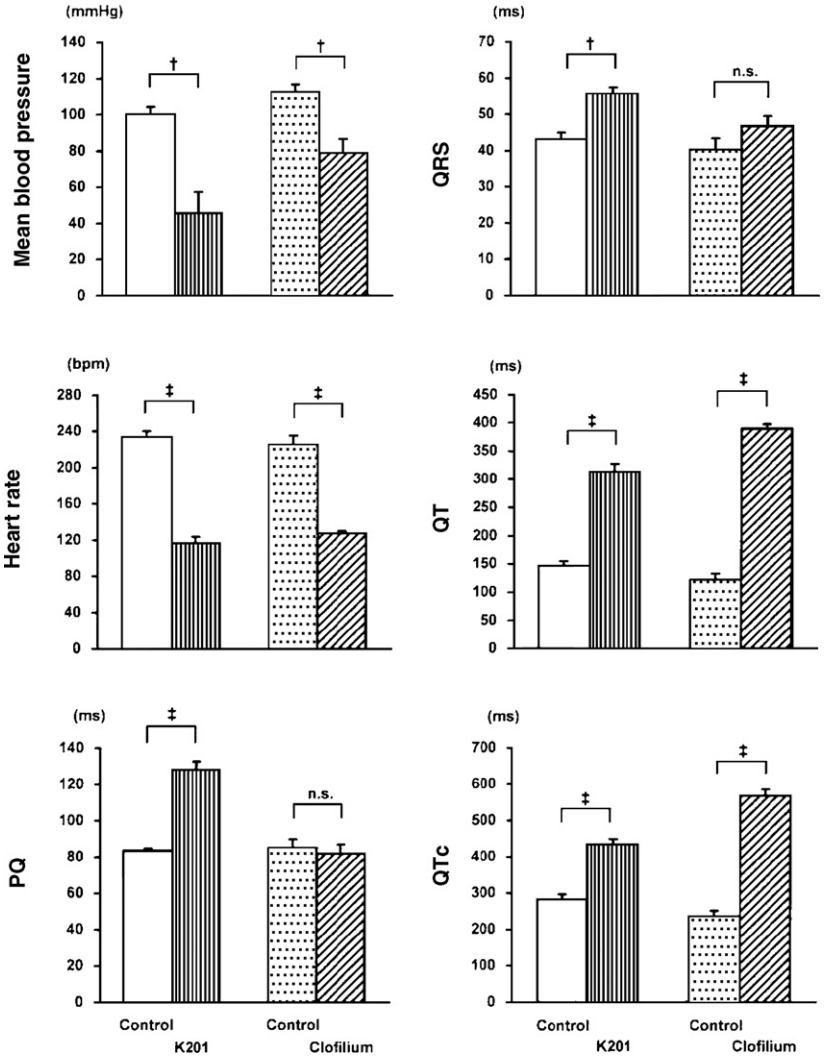

Fig. 3. Effects of clofilium and K201 with methoxamine on mean blood pressure, heart rate, PQ, QRS, QT and QTc intervals. Clofilium and K201 significantly decreased the mean blood pressure and heart rate, and increased the QT and QTc intervals, respectively. K201 prolonged the PQ and QRS intervals, but clofilium did not prolong these intervals. †;$P<0.005$, ‡;$P<0.001$, n.s.; not significant.

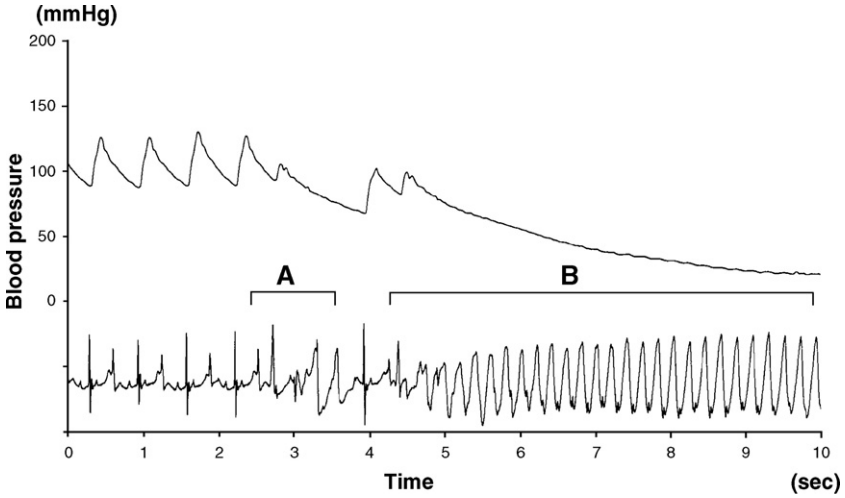

Fig. 4. Blood pressure and ECG findings for administration of clofilium with methoxamine. A; polymorphic ventricular arrhythmia, B; torsades de pointes.

for MAC; BIOPAC System). In each group, mean blood pressure, heart rate, and PQ, QRS, QT and QTc intervals were measured every 5 min for 30 min. Bazett's formula (QT/$\sqrt{}$RR interval) was used to correct the QT interval (Bazett, 1920).

Polymorphic ventricular arrhythmia was defined as fewer than 6 consecutive beats (2–5 beats), and torsades de pointes was defined as at least 6 consecutive beats of polymorphic ventricular tachycardia (Mazur et al., 1999). The incidence of premature ventricular complex was not investigated: a premature ventricular complex is characterized by the premature occurrence of a QRS complex that is abnormal in shape and has a duration that is generally longer than 120 ms (Olgin and Zipes, 2005). Premature ventricular complex, polymorphic ventricular arrhythmia, the third-degree atrioventricular block and torsades de pointes were excluded in analysis of the parameters.

Each data point in the statistical analysis represents a mean± standard error (S.E.M). Data analysis was performed using an analysis of variance (ANOVA) followed by Dunnett's test, Mann–Whitney *U* test, Fisher's exact test, an unpaired Student *t*-test and Welch's *t*-test, and differences with $P<0.05$ were considered significant.

3. Results

Administration of K201 without α_1-adrenoceptor stimulation by methoxamine caused dose-dependent prolongation of the QT and QTc intervals (Fig. 2). Administration of K201 at concentrations of 200 and 400 μg/kg/min for 30 min significantly prolonged the QT interval by 186.4±31.3% and 252.5± 37.2%, respectively, compared to the control group ($P<0.05$ and $P<0.05$, respectively, vs. control). Administration of K201 at 400 μg/kg/min also prolonged the QTc interval by 144.5± 23.0%. Infusion of K201 at 400 μg/kg/min with methoxamine resulted in prolongation of the QT and QTc intervals by 239± 15.1% and 154.1±5.4%, respectively. There were no significant differences in the QT and QTc intervals with K201 at 400 μg/kg/min in the presence and absence of methoxamine, and neither torsades de pointes nor polymorphic ventricular arrhythmia was induced by infusion of K201 with and without methoxamine.

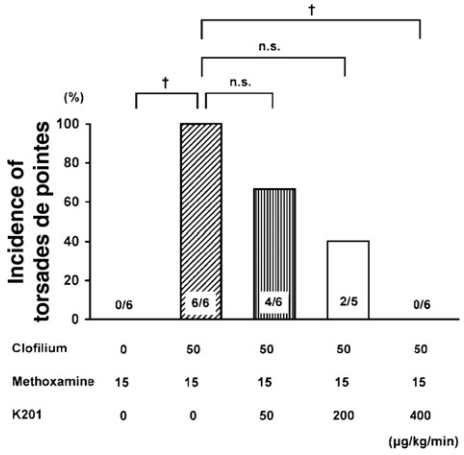

Fig. 5. Incidence of torsades de pointes. K201 inhibited the incidence of torsades de pontes dose-dependently and 400 μg/kg/min K201 completely inhibited torsades de pontes. †;$P<0.005$, n.s.; not significant.

Table 1
Number of events of torsades de pointes

Clofilium	(μg/kg/min)	50	50	50	50	0	0
Methoxamin	(μg/kg/min)	15	15	15	15	15	0
K201	(μg/kg/min)	0	50	200	400	400	400
Rabbit No	1	19	3	4	0	0	0
	2	42	0	0	0	0	0
	3	2	10	2	0	0	0
	4	1	10	0	0	0	0
	5	12	0	0	0	0	0
	6	5	1		0	0	0
Total		81	24	6	0	0	0
		(*n*=6)	(*n*=6)	(*n*=5)	(*n*=6)	(*n*=6)	(*n*=6)
Mean±S.E.M.		13.5± 6.3	4.0± 1.9[a]	1.2± 0.8[a]	0±0[b]	0±0[b]	0±0[b]

[a] not significant vs. clofilium+methoxamine group.
[b] $P<0.05$ vs. clofilium+methoxamine group.

Table 2
Number of events of polymorphic ventricular arrhythmia

Clofilium	(μg/kg/min)	50	50
Methoxamine	(μg/kg/min)	15	15
K201	(μg/kg/min)	0	400
Rabbit No	1	57	0
	2	20	0
	3	16	0
	4	126	0
	5	10	0
	6	10	0
Total		239	0
Mean±S.E.M.		39.8±18.7	0±0
Incidence		6/6	0/6 [a]

[a] $P<0.05$ vs. clofilium+methoxamine group.

Changes in hemodynamic and ECG parameters were investigated for concomitant administration of methoxamine with either K201 at 400 μg/kg/min or clofilium at 50 μg/kg/min (Fig. 3). With K201 the mean blood pressure and heart rate showed significant decreases to 45.7±11.6 mmHg and 116.7±7.0 bpm, respectively ($P<0.005$ and $P<0.001$, respectively, vs. control), and significant prolongation of the PQ, QRS, QT and QTc intervals to 128.2±4.5, 55.7±1.8, 313.2±14.0 and 433.5±15.3 ms, respectively.

With clofilium, there was significant prolongation of the QT and QTc intervals to 389.5±8.4 and 568.3±17.4 ms, respectively, but no significant prolongation of the PQ and QRS intervals. All animals receiving clofilium with methoxamine showed polymorphic ventricular arrhythmia (Fig. 4A) and torsades de pointes (Fig. 4B), with a decrease of blood pressure. Administration of 0, 50, 200 and 400 μg/kg/min K201 to animals receiving clofilium and methoxamine gave an incidence of torsades de pointes of 100% (6/6), 67% (4/6), 40% (2/5) and 0% (0/6), respectively (Fig. 5); therefore, K201 showed dose-dependent inhibition of torsades de pointes induced by clofilium with methoxamine, and 400 μg/kg/min K201 suppressed torsades de pointes completely, despite causing QT prolongation. K201 at concentrations of 0, 50, 200 and 400 μg/kg/min also inhibited the number of events of torsades de pointes, which were 13.5±6.3, 4.0±1.9, 1.2±0.8 and 0±0, respectively (Table 1), and the number of events of polymorphic ventricular arrhythmia was also significantly inhibited by K201 (Table 2).

K201 at 400 μg/kg/min significantly attenuated an increase in repolarization caused by 50 μg/kg/min clofilium with

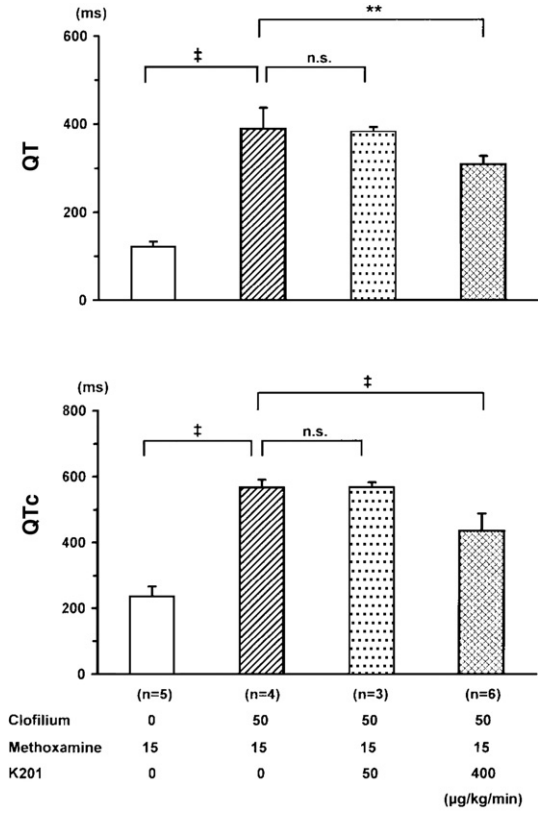

Fig. 6. QT and QTc intervals after 30 min of administration of K201 under the experimental protocol in Section 2.2.3. 50 μg/kg/min K201 did not attenuate prolongation of QT and QTc intervals, but 400 μg/kg/min K201 significantly decreased prolongation. **;$P<0.01$, ‡;$P<0.001$, n.s.; not significant.

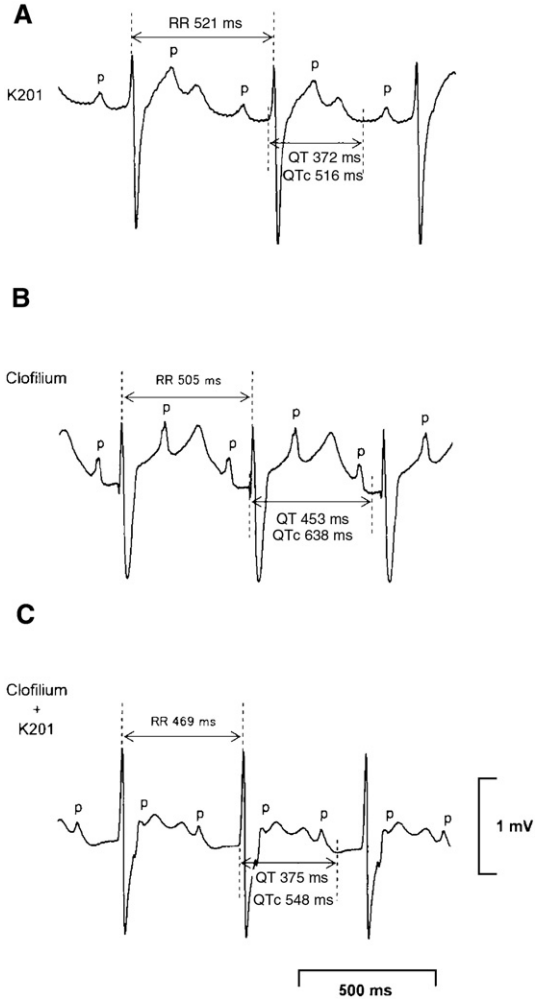

Fig. 7. Representative ECG findings in the presence of methoxamine over 25 min, showing QT and QTc intervals after administration of 400 μg/kg/min K201 (A), 50 μg/kg/min clofilium (B) and 50 μg/kg/min clofilium+400 μg/kg/min K201 (C). All ECG data are shown under conditions of 2:1 atrioventricular block.

methoxamine. QT intervals with K201 and clofilium, and with clofilium were 309±19 and 389±49 ms, respectively ($P<0.01$), and QTc intervals were 435±23 and 568±54 ms, respectively, showing a significant decrease in QTc interval with K201 compared to clofilium ($P<0.001$) (Fig. 6). Representative ECGs during infusion of methoxamine and administration of K201, clofilium, and clofilium with K201 are shown in Fig. 7A, B and C, respectively. These data show that K201 decreased an increase in QT prolongation caused by clofilium.

4. Discussion

Drugs that prolong the QT interval sometimes induce torsades de pointes and ventricular fibrillation, with an accompanying risk of sudden death (Zipes and Wellens, 1998; Straus et al., 2006). Drugs that prolong the action potential duration by blocking potassium currents are referred to as class III antiarrhythmics (Nobe et al., 1993), and infusion of a low dose of class III antiarrhythmic agents and non-cardiac drugs can prolong the QT interval and induce torsades de pointes (Thibault and Nattel, 1999; Bednar et al., 2001). Administration of the class III antiarrhythmic agent clofilium with α_1-adrenoceptor stimulation leads to marked prolongation of the QT interval and occurrence of polymorphic ventricular tachycardia in rabbits, with these features being indistinguishable from clinically observed torsades de pointes (Carlsson et al., 1990).

In this study, the effects of K201 on the QT interval and proarrhythmic activity were investigated in rabbits under conditions of α_1-adrenoceptor stimulation or no stimulation. The antiarrhythmic activity of K201 was also studied in a well-established model of torsades de pointes (Carlsson et al., 1990). High-dose infusion of K201 at more than 200 μg/kg/min resulted in significant prolongation of the QT interval with and without α_1-adrenoceptor stimulation, and torsades de pointes was not induced by infusion of K201. We have also reported that infusion of a low dose of K201 (10 and 20 μg/kg/min) for 6 h without α_1-adrenoceptor stimulation does not induce torsades de pointes, although the QT interval showed significant prolongation with infusion of K201 at 20 μg/kg/min for 6 h (Matsuda et al., 2006).

The antiarrhythmic effects of K201 were also investigated in a clofilium-induced model of torsades de pointes. Clofilium in combination with α_1-adrenoceptor stimulation markedly increased the QT and QTc intervals, and under these conditions torsades de pointes was induced in all 6 animals. K201 significantly inhibited torsades de pointes in a dose-dependent manner: the incidence of torsades de pointes at K201 doses of 0, 50, 200 and 400 μg/kg/min was 100% (6/6), 67% (4/6), 40% (2/5) and 0% (0/6), respectively. At a concentration of 400 μg/kg/min K201 completely inhibited torsades de pointes and polymorphic ventricular arrhythmia. Prolongation of the QT interval due to clofilium was also significantly attenuated by K201. In this context, we note that ranolazine, an antianginal agent, exerts its effect on action potential duration more through inhibition of the late I_{Na} current, rather than blocking of I_{Kr} (Antzelevitch et al., 2004; Wu et al., 2004, 2006); therefore, the attenuation of clofilium-induced QT prolongation by K201 may be related to effects on the late I_{Na} current.

Administration of K201 resulted in significant prolongation of the PQ and QRS intervals through a calcium and sodium blocking effect, respectively, whereas clofilium did not show prolongation of these intervals. K201 also caused decreases in mean blood pressure and heart rate, showing that K201 does not have positive inotropic activity. The decrease in blood pressure suggests that K201 may have α_1-blocking effects. Many studies have shown that K201 possesses multiple pharmacological properties, including an α_1-blocking effect (Kaneko, 1994), multi-channel blocking effects (Kimura et al., 1999; Kiriyama et al., 2000; Nakaya et al., 2000), and inhibition of annexin V–Ca^{2+} channel activity (Kaneko et al., 1997). It has also been reported K201 prevents diastolic calcium leakage and ventricular tachyarrhythmia by increasing the affinity of calstabin-2 for the ryanodine receptor-2 (Wehrens et al., 2004; Wehrens and Marks, 2004; Farr and Basson, 2004).

Clofilium-induced torsades de pointes is increased by α_1-adrenoceptor stimulation and inhibited by an α_1-blocking agent, prazosin, whereas a β-blocking agent, propranolol, is ineffective in this respect (Carlsson et al., 1990). Stimulation of myocardial α_1-adrenoreceptors causes elevation of free cytosolic calcium levels via increased turnover of phosphatidylinositols (Berridge, 1984). Furthermore, the low incidence of torsades de pointes caused by cisapride may partly be due to binding of this agent to the α_1-adrenoceptor (Carlsson et al., 1997). We have reported that K201 has α_1-blocking activity (Kaneko, 1994). Inhibition of clofilium-induced torsades de pointes by K201 may be due to an α_1-blocking effect.

Bazett's formula is widely used to adjust the QT interval, but this formula has some limitations in that it tends to overcorrect at high heart rate and undercorrect at low heart rate (De Ponti et al., 2002). However, other formulae and methods for correcting QT interval also have limitations (Mirvis and Goldberger, 2005). As a limitation of this study, the QTc interval with 2:1 atrioventricular block may be undercorrected and the *P* wave may have a potent influence on the QT interval.

In summary, our results show that K201 with and without α_1-adrenoceptor stimulation causes prolongation of the QT and QTc intervals. K201 does not induce torsades de pointes, despite prolongation of the QT interval, and inhibits clofilium-induced torsades de pointes and attenuates an increase in repolarization. These results show that prolongation of the QT interval alone is not a proarrhythmic signal.

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