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Effects of tedisamil (KC-8857) on cardiac electrophysiology and ventricular fibrillation in the rabbit isolated heart

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1 The direct cardiac electrophysiological and antifibrillatory actions of tedisamil (KC-8857) were studied in rabbit isolated hearts.

2 Tedisamil (1, 3, and 10 μM), prolonged the ventricular effective refractory period (VRP) from 120 ± 18 ms (baseline) to 155 ± 19, 171 ± 20, and 205 ± 14 ms, respectively. Three groups of isolated hearts ($n=6$ each) were used to test the antifibrillatory action of tedisamil. Hearts were perfused with 1.25 μM pinacidil, a K_{ATP} channel activator. Hearts were subjected to hypoxia for 12 min followed by 40 min of reoxygenation. Ventricular fibrillation (VF) developed during hypoxia and reoxygenation in both the control and 1 μM tedisamil-treated groups (5/6 and 4/6, respectively). Tedisamil (3 μM) reduced the incidence of VF (0/6, $P=0.007$ *vs.* control).

3 In a separate group of hearts, VF was initiated by electrical stimulation. The administration of 0.3 ml of 10 mM tedisamil, *via* the aortic cannula, terminated VF in all hearts, converting them to normal sinus rhythm.

4 Tedisamil (3 μM) reversed pinacidil-induced negative inotropic effects in rabbit isolated atrial muscle which were equilibrated under normoxia, as well as in atrial muscle subjected to hypoxia and reoxygenation.

5 The results demonstrate a direct antifibrillatory action of tedisamil *in vitro*. The mechanism responsible for the observed effects may involve modulation by tedisamil of the cardiac ATP-regulated potassium channel, in addition to its antagonism of I_K and I_{to}.

Keywords: Class III antiarrhythmics; arrhythmia; K_{ATP}-regulated channel blocker; chemical defibrillation; myocardial ischaemia; potassium currents

Introduction

In experimental studies and clinical trials, Class III antiarrhythmic agents have been demonstrated to be more effective than other classes of antiarrhythmic drugs in preventing lethal ventricular arrhythmias (Lynch *et al.*, 1992; Lucchesi *et al.*, 1993; Gilman *et al.*, 1994). By prolonging the ventricular effective refractory period and action potential duration, Class III antiarrhythmic agents abolish re-entrant impulses and prevent or terminate ventricular fibrillation (Sanguinetti, 1992; Uprichard & Lucchesi, 1994). Currently available Class III drugs (amiodarone and sotalol) not only block K^+ currents in the heart, but also act on other ion channels and/or receptors causing unwanted effects (Sanguinetti, 1992). Recently developed Class III antiarrhymthmic agents, such as sematilide, MS-551, E-4031, and dofetilide (UK 68,798), selectively block the delayed rectifier K^+ current (I_K), but the reverse use-dependence properties of these agents could limit their therapeutic utilily (Hondeghem & Snyders, 1990; Baskin *et al.*, 1991; Nakaya *et al.*, 1993; Sager *et al.*, 1993). Thus, the search for new compounds in this class as well as compounds targeting other types of K^+ channels remains an important area of investigation.

Recent studies have shown that blockade of the transient outward current (I_{to}) and inward rectifier K^+ current (I_K), both of which are involved in the repolarization of the action potential (Carmeliet, 1992a), contribute to antiarrhythmic and antifibrillatory actions (Beatch *et al.*, 1991; Rees & Curtis, 1993). Tedisamil (KC-8857; 3,7-di-(cyclopropylmethyl)-9, 9-tetramethylene-3, 7-diazabicyclo [3.3.1]-nonanedihydrochloride) is a bradycardic agent and a putative I_{to} blocker. In rat isolated ventricular mycocytes, tedisamil, at low concentrations (1-20 μM), selectively suppressed I_{to} and prolonged action potential duration (Dukes & Morad, 1989; Dukes *et al.*, 1990). Tedisamil had no significant effects on the inward rectifier K^+ current, or inward Ca^{2+} current in rat or guinea-pig ventricular myocytes and blocked the Na^+ current only at concentrations above 20 μM (Dukes & Morad, 1989; Dukes *et al.*, 1990). In both conscious and anaesthetized rats, tedisamil (i.v.) lengthened the ventricular effective refractory period, action potential duration, QT interval, and reduced the incidence of ventricular fibrillation induced by coronary artery ligation. In addition, tedisamil caused bradycardia and increased systemic blood pressure (Howard *et al.*, 1989; Beatch *et al.*, 1990; 1991). The antifibrillatory effects and associated electrophysiological actions of tedisamil have been examined *in vivo* (Beatch *et al.*, 1990; 1991) as well as in rat isolated hearts (Tsuchihashi & Curtis, 1991), a species in which I_{to} is the predominant repolarization current (Josephson *et al.*, 1984; Dukes & Morad, 1989).

The present study explores the electrophysiological properties of tedisamil, and more importantly, demonstrates the antifibrillatory effects of tedisamil in a species possessing both functional I_{to} and I_K in the ventricular myocardium (Giles & Imiazumi 1988; Hiraoka & Kawano, 1989; Carmeliet, 1993; de Lorenzi *et al.*, 1994). We used the rabbit isolated heart model in the present study to determine the direct, concentration-dependent effects of tedisamil on the ventricular effective refractory period and atrioventricular node conduction because, like the rat, the rabbit myocardium contains prominent, functional I_{to} and I_K. In addition, the effects of tedisamil were examined in two models: prevention of hypoxia/reoxygenation/pinacidil-induced ventricular fibrillation and reversal of electrically-induced ventricular fibrillation.

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Methods

The studies were performed in accordance with the guidelines of the 'University of Michigan Committee on the Use and Care of Animals'. The animal care and use programme conforms to the standards in 'The Guide for the Care and Use of Laboratory Animals', DHEW Publ. No. (NIH) 86–23.

Langendorff perfused isolated heart preparation

New Zealand white rabbits (2.1–2.5 kg) were randomized to different experimental groups. All rabbits were killed by cervical dislocation. The hearts were removed rapidly and prepared for perfusion by the Langendorff method using a modified Krebs-Henseleit buffer. Coronary artery perfusion was maintained with the use of a roller pump adjusted to produce a mean coronary artery perfusion pressure of 40 ± 5 mmHg (20 ± 2 ml min^{-1}) maintained throughout the experimental protocol. The hearts were paced at a frequency of 10–20% above their intrinsic sinoatrial rate. The pacing stimulus was provided by a Grass SD5 (Grass Instrument Company, Quincy, MA, U.S.A.) pulse generator and applied to the right atrium *via* bipolar electrodes. The pacing stimulus was set at 10% above threshold voltage and a pulse duration of 4 ms. A cannula with a latex balloon at its distal end was inserted through the left atrium, across the mitral valve and placed in the left ventricle. The proximal end of the cannula was connected to a pressure transducer for recording left ventricular systolic and end-diastolic pressures. The balloon was expanded with distilled water to establish a ventricular end-diastolic pressure of 5 mmHg. The volume in the intraventricular balloon was maintained constant throughout the course of each experiment. A polyethylene cannula was placed in the left ventricle to vent the chamber. A thermistor probe (Tele-thermometer, Yellow Springs Instrument Co. Yellow Springs, OH, U.S.A.) was inserted in the left ventricle to monitor the temperature of the heart. The electrogram was recorded by electrodes attached to the aorta and apex of the heart. A pressure transducer was connected to a side arm of the aortic cannula to monitor the coronary artery perfusion pressure (CPP). The left ventricular pressure (LVP), the first derivative of the left ventricular pressure ($\pm dP/dt$), electrogram and coronary perfusion pressure (CPP) were recorded with a Grass Model 7 polygraph (Grass Instrument Company, Quincy, MA, U.S.A.).

The hearts were equilibrated for 30 to 40 min before each experiment and perfused without recirculating the buffer. The temperature of the buffer was maintained constant at 37°C. The buffer was prepared daily and adjusted to pH 7.4. The perfusion medium was circulated through an 'artificial lung' consisting of 6 metres of medical grade, gas permeable tubing (Silastic, Dow Corning Corp, Midland, MI, U.S.A.) placed in a water-heated chamber. The chamber was gassed continuously with 95% O_2/5% CO_2 to generate a Po_2 of approximately 500 mmHg in the perfusion medium.

Experimental protocols

Protocol I: Electrophysiology The effects of tedisamil on the ventricular excitation threshold voltage (VET), ventricular refractory period (VRP) and atrioventricular conduction were determined in 9 isolated hearts perfused with a modified Krebs-Henseleit buffer to the following composition (mmol l^{-1}): NaCl 117, KCl 4.0, $CaCl_2.H_2O$ 2.4, $MgCl_2.6H_2O$ 1.2, $NaHCO_3$ 25, KH_2PO_4 1.1, glucose 5.0, monosodium L-glutamate 5.0, and sodium pyruvate 2.0. The final concentration of K^+ in the perfusion medium was 5.1 mM. A miniature bipolar plunge electrode (INAPRES, Norwich, NY, U.S.A.) was attached to the right ventricular outflow tract (RVOT) for delivery of the S_2 ventricular stimulus from a Grass S8800 square wave stimulator and stimulus isolation unit (SIU5; Grass Instrument Company, Quincy, MA, U.S.A.). The S_2 stimulus, with a duration of 4 ms, was triggered 250 ms after the 'R wave' of the electrogram. The excitation threshold voltage was defined as the minimum voltage required to elicit a propagated ventricular impulse. The refractory period determined in the region of RVOT is defined as the longest R-wave to S_2 stimulus interval that failed to elicit a propagated ventricular complex at 1.5 times threshold voltage. The P–R interval was determined from the electrogram recording. After a 60 min period of equilibration, the hearts were perfused with buffer containing 0.1, 1, 3 or 10 μM tedisamil. Electrophysiological parameters were determined 15 min after exposure to each concentration of tedisamil. Figure 1a illustrates the experimental protocol.

Protocol 2: Hypoxia/reoxygenation and pinacidil-induced ventricular fibrillation (Figure 1) A total of 22 rabbit isolated hearts were used in this portion of the experiment, from which 4 hearts were excluded before entering the protocol due to technical failures. Eighteen hearts were randomly allocated to three experimental groups: control, $n=6$; tedisamil (1 μM), $n=6$; tedisamil (3 μM), $n=6$. After 30 to 40 min of equilibration, the isolated hearts were perfused with buffer containing drug-vehicle solution (control) or tedisamil (1 μM and 3 μM) for 10 min followed by pinacidil (1.25 μM), an ATP-regulated K^+ (K_{ATP}) channel opener, added to the buffer. Five min after the addition of pinacidil, the hearts were subjected to 12 min of perfusion under hypoxic conditions by changing the gas mixture in the 'artificial lung' to 95%N_2/5%CO_2. At the end of the hypoxic perfusion period, normoxic perfusion of the heart was reinstituted (reoxygenation) and maintained for 40 min. The cardiac electrogram, coronary perfusion pressure and left ventricular function were monitored continuously. The endpoint of the experiment was defined as the occurrence of sustained ventricular fibrillation during hypoxia and/or reoxygenation. The composition of the buffer perfusate in this protocol had the following composition (in mmol l^{-1}): NaCl 117, KCl 1.4, $CaCl_2.H_2O$ 2.4, $MgCl_2.6H_2O$ 1.2, $NaHCO_3$ 25, KH_2PO_4 1.1, glucose 5.0, monosodium L-glutamate 5.0 and sodium pyruvate 2.0. The final concentration of K^+ in the perfusion medium was 2.5 mM.

Protocol 3: Tedisamil and chemical defibrillation To determine whether tedisamil could terminate sustained ventricular fibrillation, a separate group of 9 hearts were examined. Hearts in this protocol were perfused with a modified Krebs-Henseleit buffer with the same composition as described in protocol 1. Sustained ventricular fibrillation was induced by a train of electrical stimuli delivered through a

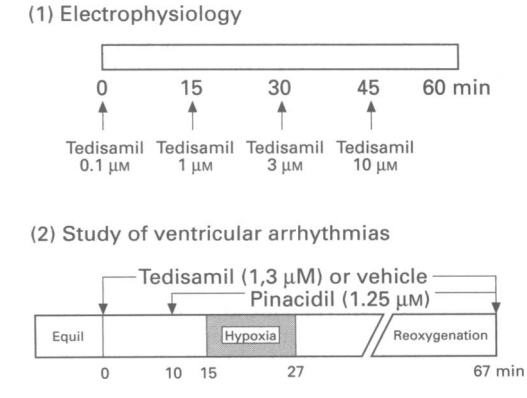

Figure 1 Schematic experimental protocols used in the rabbit isolated heart study. Protocol 1 was used to examine the direct electrophysiological effects of tedisamil at various concentrations. All electrophysiological parameters were recorded 15 min after the exposure to each concentration of tedisamil. Protocol 2 was used to determine the ability of tedisamil to prevent hypoxia-induced ventricular fibrillation in the presence of pinacidil.

miniature bipolar plunge electrode (INAPRES, Norwich, NY, U.S.A.) secured over the right ventricular outflow tract (RVOT) for delivery of the S_2 ventricular stimulus from a Grass S8800 square wave stimulator and stimulus isolation unit (SIU5; Astro-Med Inc., West Warwick, RI, U.S.A.). The S_2 stimulus duration was 4 ms and was triggered after the 'R wave' of the electrogram. Hearts received a train of stimuli delivered to the region of the RVOT (S2, S3, S4-instead of a single impulse) until ventricular fibrillation occurred. Typical ventricular fibrillation induction parameters included a pulse level of 7–10 V, a pulse delay of 100–150 ms, a pulse interval of 90–100 ms, a pulse duration of 4.0 ms, and a train duration of 200–500 ms. Ventricular fibrillation was sustained for 30 s, at which time 0.3 ml of vehicle (buffer) was injected through a sideport of the aortic cannula. After an additional 30 s had elapsed, either vehicle or tedisamil (0.3 ml or 0.6 ml of 1 mM drug, or 0.3 ml of 10 mM drug) was administered. The time from the second injection to reversal to normal sinus rhythm was recorded.

Rabbit isolated atrial muscle preparation Rabbit atria (1 cm long, 3 mm wide and 2 mm thick) were excised from rabbit isolated hearts and quickly placed in oxygenated, 37°C, modified Krebs-Henseleit buffer of the same composition as described in protocol 1. The muscle preparations were in contact with a pair of platinum electrodes and fixed at one end in a spring-loaded clamp. The other end of the tissue was attached to a calibrated force displacement transducer (Grass Instrument Co., Quincy MA, U.S.A., Model FT.03C). The electrical signal from the displacement transducer was amplified and recorded with a Grass Polygraph. The atrial tissue was stimulated with a Grass S88 square wave generator at a frequency of 1.5 Hz, a pulse duration of 4 ms at twice the minimum threshold voltage. The tissue was preloaded with 4 g of tension by adjusting the height of the force displacement transducer.

The isolated muscle preparations were allowed to equilibrate for 60 min under normoxia (95% O_2/5% CO_2) or 20 min under hypoxia (95% N_2/5% CO_2) followed by 40 min reoxygenation ($n=10$ in each group), during which time the bathing media was replaced three times. The experimental protocol was begun after a steady state of isometric force development had been achieved. The concentration-response relationship for the negative inotropic action of pinacidil was established by a cumulative increase in the concentration of pinacidil in the bathing media. There was a 5 min interval between each increment in drug concentration to allow a new steady state response to develop. To determine if tedisamil could reverse pinacidil-induced negative inotropy, tedisamil (3 μM) was added to the bathing media after the final concentration of pinacidil had been achieved in the bath. Thereafter, the recovery of muscle tension was monitored for 5 min. The change in isometric tension was determined and expressed as a percentage of the pre-drug, baseline value.

Materials

Tedisamil hydrochloride (KC-8857; 3,7-di-(cyclopropylmethyl)-9,9-tetramethylene-3,7-diazabicyclo[3.3.1]nonane dihydrochloride, Figure 2) was supplied by Solvay Pharmaceuticals (Germany). All other materials were purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.) unless otherwise specified.

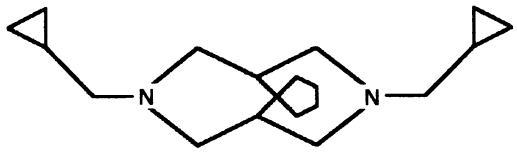

Figure 2 Chemical structure of tedisamil (KC-8857) (3,7-di-(cyclopropylmethyl)-9,9-tetramethylene-3,7-diazabicyclo[3.3.1]nonane dihydrochloride).

Data analysis

The data are expressed as mean ± s.e. mean. The difference in the incidence of ventricular fibrillation among groups was analyzed by Fisher's Exact test. ANOVA (factorial) was used for comparisons between groups at specific time points. ANOVA (repeated measures), followed by a Fisher's protected least significant difference (PSLD) *post hoc* test was used for comparisons over time within groups. Statistical significance was established as a probability of <0.05.

Results

Electrophysiological action of tedisamil

After 60 min of equilibration, hearts were perfused with buffer containing 0.1, 1, 3 and 10 μM tedisamil. Electrophysiological parameters were determined 15 min after exposure to each concentration of tedisamil (Figure 1). Figure 3 is an example of S_2 stimulation and induced PVCs during the determination of VET and VRP. Tedisamil, at a concentration of 1, 3 and 10 μM, prolonged VRP from a mean baseline value of 120±18 ms to 155±19 ms, 171±20 ms, and 205±14 ms, respectively (Figure 4). The VET was increased by 1, 3 and 10 μM tedisamil, but reached statistical significance at 3 μM compared to baseline value (Figure 4). A significant prolongation of P-R interval was observed after 1, 3 and 10 μM tedisamil treatment (from a mean baseline value of 76±4 ms to 86±5 ms, 103±4 ms and 139±13 ms, respectively, Figure 4). A 2:1 A–V conduction block or atrioventricular dissociation occurred in 6 out of 7 hearts treated with 10 μM tedisamil. Figure 5 is an original recording from one experiment depicting the concentration-dependent prolongation of P-R interval and 2:1 A-V blockade at a tedisamil concentration of 10 μM.

Prevention of ventricular fibrillation

One group of hearts was used as a control group while the other two groups were exposed to 1 μM or 3 μM tedisamil added to the perfusion medium 10 min before the addition of pinacidil. There was a high incidence of ventricular fibrillation during hypoxia and reoxygenation in both the control group and in the group of hearts treated with 1 μM tedisamil (5/6 and 4/6, respectively). When the concentration of tedisamil was increased to 3 μM, the incidence of ventricular fibrillation was reduced significantly (0/6, $P=0.007$ *vs.* control group, by Fisher's Exact Test; Figure 6 and Table 1). Figure 6 shows the time course of occurrence of ventricular fibrillation in all groups.

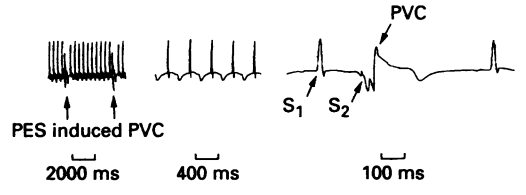

Figure 3 An original recording during the determination of the ventricular excitation threshold (VET) and ventricular effective refractory period (VRP) in the rabbit isolated heart. The premature ventricular complexes (PVCs) induced by programmed electrical stimulation (PES) are indicated. Cycle length, 400 ms; S_1S_2 interval = 169 ms; threshold voltage = 3.4 V.

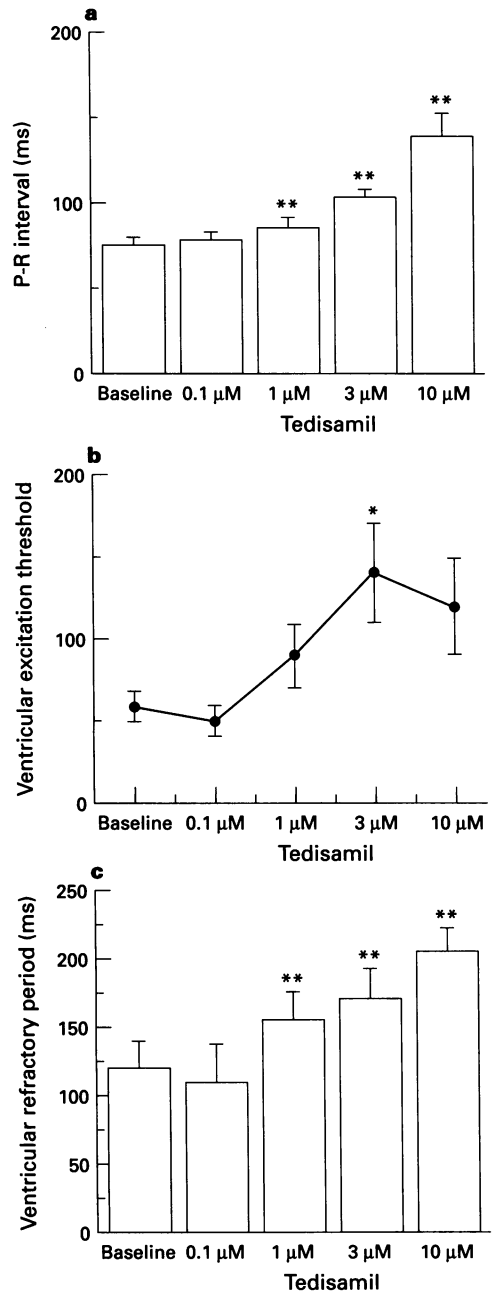

Figure 4 Tedisamil, at 1, 3, and 10 μM, prolonged the ventricular effective refractory period (VRP) (c) and P-R interval (a) in the rabbit isolated heart ($n=9$). The increase of ventricular excitation threshold (VET) (b) was significant in the presence of 3 μM tedisamil. *$P \leq 0.05$ and **$P \leq 0.01$, compared with the baseline value by paired t test in each panel. All the values were determined 15 min after each concentration of tedisamil.

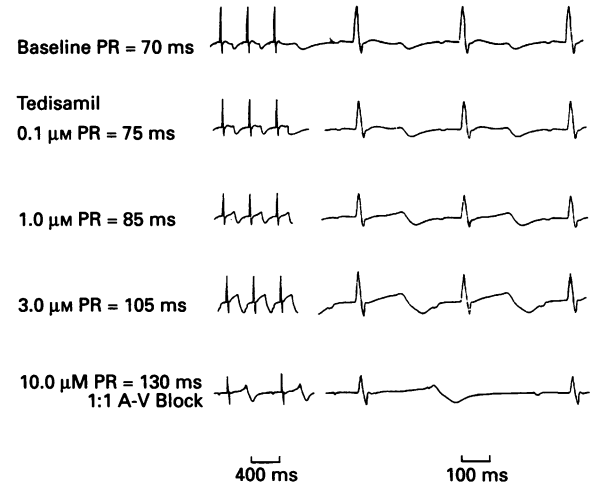

Figure 5 An example of the progressive increase of P-R interval by tedisamil in Protocol 1. The complete atrioventricular (A-V) block occurred after 10 μM tedisamil. The rabbit isolated hearts were paced *via* the right atrium. Cycle length = 400 ms.

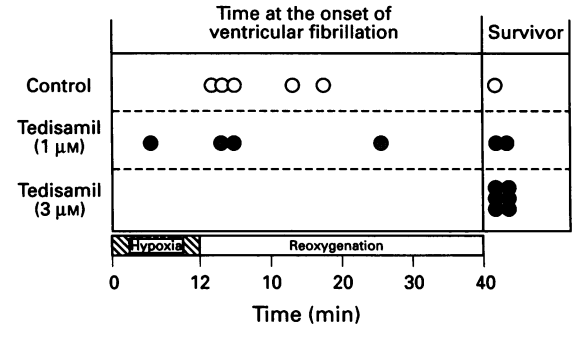

Figure 6 Time course of development of ventricular fibrillation in the hypoxic/reoxygenated rabbit isolated heart. Three groups of hearts ($n=6$ in each group) were perfused with buffer containing pinacidil (1.25 μM) for 5 min, then subjected to hypoxia for 12 min followed by 40 min of reoxygenation. Two groups of hearts were exposed to tedisamil (1 and 3 μM) 10 min before the addition of pinacidil in the perfusion medium. Ventricular fibrillation occurred in 5 of 6 hearts from the control group (without tedisamil). Tedisamil, at 3 μM, significantly reduced the incidence of ventricular fibrillation compared with that of the control group. Each symbol represents an individual isolated heart.

Table 1 Antifibrillatory action of tedisamil in rabbit isolated hearts under hypoxia/reoxygenation and pinacidil challenge

	n	*VF*	*% of VF*	P
Control	6	5	83	
Tedisamil (1 μM)	6	4	67	0.409
Tedisamil (3 μM)	6	0	0	0.007

Chemical defibrillation with tedisamil

Vehicle administration (0.3 or 0.6 ml) did not change the status (frequency or duration) of ventricular fibrillation and spontaneous reversal to sinus rhythm did not occur in any of the hearts (Figure 7). Tedisamil (0.3 or 0.6 ml of a 1 mM solution) did not terminate ventricular fibrillation, although the cycle length was prolonged, e.g. the frequency of the fibrillatory waves was reduced (data not shown). However, administration of 0.3 ml of a 10 mM tedisamil solution *terminated* ventricular fibrillation in each of the 5 hearts ($P = 0.008$ *vs.* vehicle group by Fisher's Exact Test; Figure 7). The frequency of the fibrillatory waves was reduced immediately after the drug was introduced and normal sinus rhythm was restored within 98 ± 47 s. The electrically induced ventricular fibrillation was converted to ventricular tachycardia in two hearts several seconds after tedisamil, and proceeded to normal sinus rhythm within minutes. Figure 8 is a representative tracing from a heart that was successfully defibrillated after the administration of tedisamil.

Effects of tedisamil on cardiac function

During the study of antifibrillatory effects in the three groups of hearts (*Protocol 2*), the cardiac function was monitored

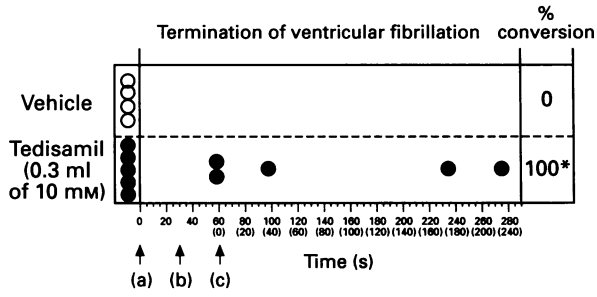

Figure 7 Time course for chemical defibrillation by tedisamil of electrically-induced ventricular fibrillation in the rabbit isolated heart. Ventricular fibrillation (VF) was induced in two sets of hearts (at a) one of which received a bolus injection of vehicle 30 (b) and 60 s (c) after induction of VF ($n=4$). The other group of hearts received a bolus injection of vehicle 30 s (b) after induction of VF and 0.3 ml of 10 mM tedisamil 60 s (c) after induction of VF. Hearts receiving vehicle only did not revert to normal sinus rhythm whereas 100% of hearts receiving tedisamil were converted to normal sinus rhythm ($P = 0.008$ compared to vehicle by Fisher's Exact Test).

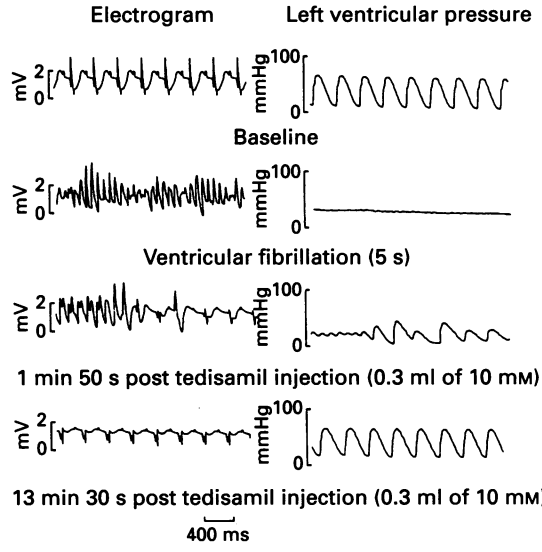

Figure 8 An example of the chemical defibrillatory effects of tedisamil in the rabbit isolated heart. Sustained ventricular fibrillation (VF) was elicited by a train of electrical stimuli applied to the RVOT. Tedisamil (0.3 ml of 10 mM) was administered to the heart through the cannulated aorta while the coronary vessels were perfused continuously with oxygenated buffer. The cycle length of the fibrillatory waves was prolonged progressively and ventricular fibrillation was converted to normal sinus rhythm after 1 min and 50 s exposure to tedisamil. Cardiac function recovered to the pre-fibrillation state 13 min after drug administration.

continuously. All hearts were paced electrically from the right atrium at a frequency of 20–30% above the intrinsic sinus rate. Heart rate is expressed as the total number of ventricular complexes and includes both the paced ventricular complexes as well as those depolarizations arising spontaneously. During the latter phase of hypoxia the heart rate was reduced in each of three groups even though atrial electrical pacing was maintained. The observed bradycardia suggests the development of atrioventricular block due to hypoxia. Hearts treated with 1 μM tedisamil demonstrated less bradycardia during hypoxia, compared to 3 μM tedisamil-treated hearts (Table 2). Normal atrioventricular conduction returned upon reoxygenation in all groups. There was no difference in heart rate among groups at respective time-points throughout the experimental procedure (Table 2).

Tedisamil, in a concentration-dependent manner, increased the coronary perfusion pressure (CPP) from a mean baseline value of 43±3 mmHg to 54±4 mmHg at 1 μM and from 37±3 mmHg to 50±3 mmHg at 3 μM after 10 min of exposure (Table 2). Both LVDP and $\pm dP/dt$ decreased to the same extent during hypoxia followed by a partial return upon reoxygenation in all experimental groups. Due to the development of ventricular fibrillation, very few hearts remained in the control group and 1 μM tedisamil-treated groups during reoxygenation, thus precluding statistical analysis of the data towards the latter part of the reoxygenated period. Tedisamil did not change any cardiac functional parameters, such as LVDP, left ventricular end-diastolic pressure (LVEDP) and left ventricular $\pm dP/dt$ throughout the experiment (Tables 3 and 4).

Rabbit isolated atrial muscle

Reversal of the pinacidil-induced negative inotropic effect The amplitude of isometric contractile force was approximately 62% of baseline after exposure to the final concentration of pinacidil (10^{-4} M) in atrial tissue equilibrated under normoxia. The subsequent addition of tedisamil (3 μM) to the bathing medium in the continued presence of pinacidil (10^{-4} M) resulted in a reversal of the pinacidil-induced negative inotropic action. The isometric-contractile force of the atrial muscle preparations recovered and achieved 86% of pre-drug baseline values after 5 min of 3 μM tedisamil exposure (Figure 9a). Similarly, contractile force in atrial tissue was approximately 67% of baseline after treatment with the final concentration of pinacidil in atrial tissue equilibrated under hypoxia/reoxygenation. The isometric-contractile force of the atrial muscle recovered to approximtely 86% of baseline contractions after treatment with 3 μM tedisamil (Figure 9b).

Discussion

Unlike calcium channel blockers and β-adrenoceptor antagonists, tedisamil does not depress ventricular contractile function while reducing heart rate (Thormann *et al.*, 1993). The blockade of K^+ outward currents and subsequent prolongation of repolarization in the sinoatrial pacemaker cells accounts for the bradycardic action of tedisamil (Dukes & Morad, 1992). The extent of QTc prolongation caused by tedisamil has been shown to be species-dependent. Tedisamil caused a significant increase in the QTc and/or prolongation of the action potential duration in rat myocardium (Beatch *et al.*, 1990). In contrast, limited QTc prolongation was observed in other species, such as dogs, guinea-pigs, rabbits, and pigs (Buschmann *et al.*, 1989). This difference may be due to the role of different K^+ channels in repolarization of the cardiac tissue in a variety of species. The antiarrhythmic and antifibrillatory effects of tedisamil have been reported mainly in rat heart models (Beatch *et al.*, 1991; Adaikan *et al.*, 1992; Bril *et al.*, 1993), a species in which I_{to} is the predominant outward repolarizing current in ventricular myocardium. In our investigation, the direct electrophysiological and antifibrillatory effects of tedisamil were investigated in rabbit isolated hearts. Two independent models were used to assess the antifibrillatory action of tedisamil.

In conscious and anaesthetized rats, Adaikan *et al.* (1992) and Beatch *et al.* (1991) reported that tedisamil (0.5–4 mg kg^{-1}, i.v.) dose-dependently lengthened the effective refractory period, the duration of epicardial intracellular action potential, and the QTc interval. Bril *et al.* (1993) reported a similar observation and suggested that specific blockade of I_{to} was responsible for the apparent Class III action of tedisamil, since the I_{Kr} (rapidly activating component of I_K) blocker, E-4031, did not change QTc interval in a similar anaesthetized rat model. Tedisamil was also shown to prolong the effective refractory period and QTc interval in anaesthetized dogs (Wallace *et al.*, 1995). In our investigation, the blockade of both I_{to} and I_K by tedisamil may be operative and responsible for the observed increases in the ventricular refractory period (Figure 4).

Table 2 Effects of tedisamil on heart rate and coronary perfusion pressure in rabbit isolated hearts

A *Heart rate*

	Baseline	*Tedisamil* (10 min)	*Pinacidil*† (5 min)	*Hypoxia* (12 min)	*Reoxygenation* (5 min)	(40 min)
Control	157 ± 3(6)	158 ± 3(5)	155 ± 4(6)	34 ± 8(6)[bcd]	150 ± 6(3)	165(1)
Tedisamil (1 μM)	157 ± 3(6)	157 ± 3(6)	157 ± 3(6)	61 ± 7(5)[abcd]	138 ± 10(3)	150 ± 0(2)
Tedisamil (3 μM)	153 ± 2(6)	153 ± 2(6)	141 ± 13(6)	45 ± 8(6)[bcd]	124 ± 17(6)[bc]	146 ± 8(6)

B *Coronary perfusion pressure*

	Baseline	*Tedisamil* (10 min)	*Pinacidil* (5 min)	*Hypoxia* (12 min)	*Reoxygenation* (5 min)	(40 min)
Control	44 ± 4(6)	47 ± 4(5)	38 ± 4(6)	56 ± 7(6)[b]	57 ± 13(3)	43(1)
Tedisamil (1 μM)	43 ± 3(6)	54 ± 4(6)[b]	53 ± 4(6)[a]	47 ± 6(5)	50 ± 3(3)	103 ± 8(2)
Tedisamil (3 μM)	37 ± 3(6)	50 ± 3(6)	45 ± 3(6)	43 ± 7(6)	49 ± 7(6)	87 ± 14(6)[bcd]

[a]$P<0.05$ *vs.* control, ANOVA; [b]$P<0.05$ *vs.* baseline; [c]$P<0.05$ *vs.* 10 min tedisamil; [d]$P<0.05$ *vs.* 5 min pinacidil, Fisher's PLSD. Values in parentheses represent numbers of hearts from which mean ± s.e. were calculated. †Pinacidil concentration = 1.25 μM.

Table 3 Effects of tedisamil on left ventricular pressure in rabbit isolated hearts

A *Left ventricular developed pressure*

	Baseline	*Tedisamil* (10 min)	*Pinacidil*† (5 min)	*Hypoxia* (12 min)	*Reoxygenation* (5 min)	(40 min)
Control	98 ± 5(6)	92 ± 3(5)	90 ± 5(6)	37 ± 7(6)[bcd]	46 ± 13(3)	70(1)
Tedisamil (1 μM)	106 ± 8(6)	105 ± 5(6)	105 ± 6(6)	25 ± 5(5)[bcd]	22 ± 10(3)	13 ± 3(2)
Tedisamil (3 μM)	97 ± 4(6)	98 ± 6(6)	99 ± 5(6)	35 ± 5(6)[bcd]	62 ± 11(6)[abcd]	71 ± 14(6)[bcd]

B *Left ventricular end diastolic pressure*

	Baseline	*Tedisamil* (10 min)	*Pinacidil* (5 min)	*Hypoxia* (12 min)	*Reoxygenation* (5 min)	(40 min)
Control	5 ± 1(6)	3 ± 2(5)	4 ± 1(6)	42 ± 8(6)[bcd]	41 ± 15(3)	23(1)
Tedisamil (1 μM)	4 ± 2(6)	3 ± 2(6)	4 ± 2(6)	48 ± 14(5)[bcd]	67 ± 16(3)	90 ± 0(2)
Tedisamil (3 μM)	3 ± 1(6)	4 ± 1(6)	4 ± 1(6)	31 ± 13(6)[bcd]	26 ± 14(6)[bcd]	27 ± 13(6)[abcd]

[a]$P<0.05$ *vs.* control, ANOVA; [b]$P<0.05$ *vs.* baseline; [c]$P<0.05$ *vs.* 10 min tedisamil; [d]$P<0.05$ *vs.* 5 min pinacidil, Fisher's PLSD. Values in parentheses represent numbers of hearts from which mean ± s.e. were calculated. †Pinacidil concentration = 1.25 μM.

Table 4 Effects of tedisamil on left ventricular pressure ± *dp/dt* in rabbit isolated hearts

+dp/dt

	Baseline	*Tedisamil* (10 min)	*Pinacidil*† (5 min)	*Hypoxia* (12 min)	*Reoxygenation* (5 min)	(40 min)
Control	1500 ± 78(5)	1560 ± 51(5)	1280 ± 86(5)[c]	640 ± 103(5)[bcd]	650 ± 226(3)	1200(1)
Tedisamil (1 μM)	1550 ± 87(4)	1613 ± 83(4)	1588 ± 66(4)[a]	633 ± 176(3)[bcd]	450 ± 250(2)	200 ± 1
Tedisamil (3 μM)	1410 ± 93(5)	1530 ± 122(5)	1410 ± 93(5)	660 ± 81(5)[bcd]	850 ± 160(5)[bcd]	1100 ± 243(5)[c]

−dp/dt

	Baseline	*Tedisamil* (10 min)	*Pinacidil* (5 min)	*Hypoxia* (12 min)	*Reoxygenation* (5 min)	(40 min)
Control	1060 ± 189(5)	1040 ± 197(5)	870 ± 208(5)	370 ± 80(5)[bcd]	400 ± 0(3)	650(1)
Tedisamil (1 μM)	950 ± 104(4)	963 ± 103(4)	938 ± 103(4)	250 ± 50(3)[bcd]	300 ± 100(2)	200(1)
Tedisamil (3 μM)	890 ± 51(5)	970 ± 44(5)	940 ± 40(5)	300 ± 45(5)[bcd]	455 ± 73(5)[bcd]	620 ± 120(5)[bcd]

[a]$P<0.05$ vs. control, ANOVA; [b]$P<0.05$ vs. baseline; [c]$P<0.05$ vs. 10 min tedisamil; [d]$P<0.05$ vs. 5 min pinacidil, Fisher's PLSD. Values in parentheses represent numbers of hearts from which mean ± s.e. were calculated. †Pinacidil concentration = 1.25 μM.

When rabbit isolated hearts were perfused in the presence of pinacidil, a high incidence of spontaneous and sustained ventricular fibrillation occurred during hypoxic perfusion or during reoxygenation, which was significantly reduced in the presence of 3 μM tedisamil (Figure 6). Shortening of action potential duration, reduction of refractory period and initiation of re-entry are precursors to the onset of ventricular fibrillation (Chi *et al.*, 1993; Fagbemi *et al.*, 1993). Several K^+ channel blockers, such as glibenclamide, E-4031, clofilium (Friedrichs *et al.*, 1994) and ibutilide (Friedrichs *et al.*, 1993), effectively prevented the development of ventricular fibrillation in this model. *In vivo* studies reveal that tedisamil prevents regional ischaemia- and reperfusion-induced ventricular fibrillation in anaesthetized and conscious rats (Beatch *et al.*, 1991; Adaikan *et al.*, 1992; Bril *et al.*, 1993). It was proposed that tedisamil increased refractoriness, which resulted in an extension of path lengths such that the multiple re-entry circuits that contribute to the development and maintenance of

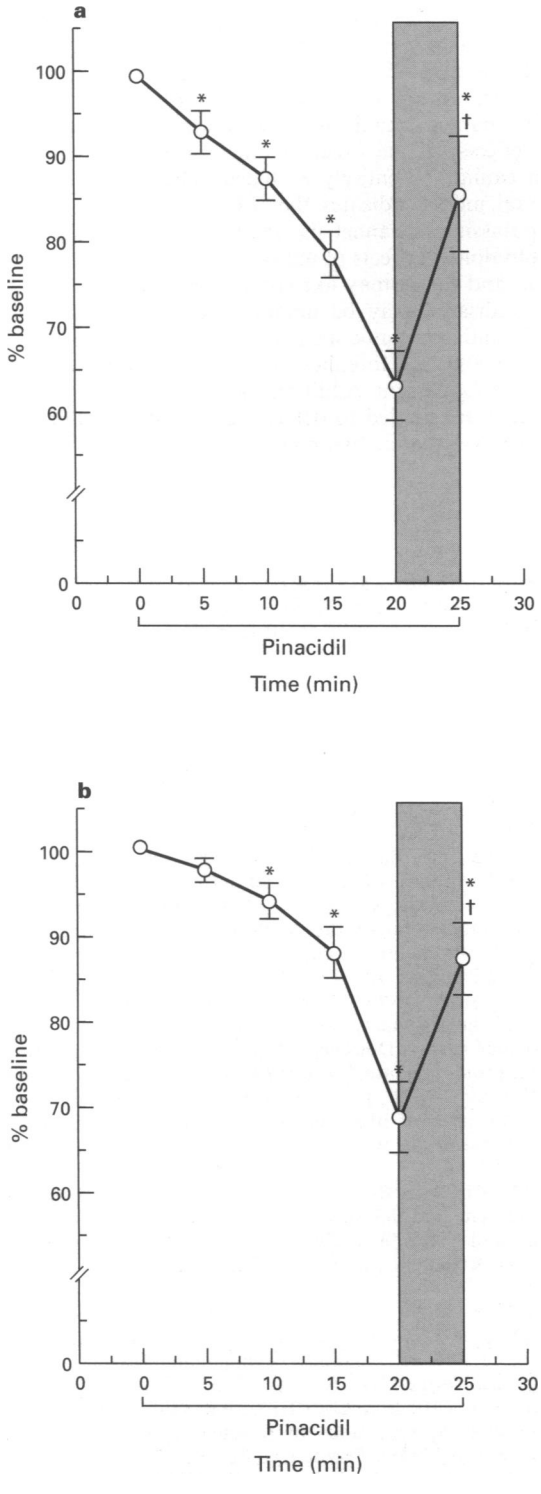

Figure 9 (a) Represents the recovery of atrial muscle contractile force after the addition of tedisamil to the pinacidil (10^{-4} M)-depressed rabbit atrial muscle preparation ($n=10$) which was equilibrated under normoxic conditions. Tedisamil (3 μM) reversed the negative inotropic effect of pinacidil in the rabbit isolated atrial muscle preparation which is represented in the figure by the shaded area. *$P \leqslant 0.05$ compared to baseline using a paired t test $^{\dagger}P \leqslant 0.05$ compared to 3×10^{-4} M pinacidil using a paired t test. (b) Depicts a pinacidil-induced (1×10^{-5} M to 3×10^{-4} M) concentration-dependent negative inotropic effect on rabbit isolated atrial tissue ($n=10$) which was equilibrated during 20 min of hypoxia followed by 40 min of reoxygenation. Tedisamil (3 μM) restored approximately 85% of pre-pinacidil isometric contraction, which is represented in the figure by the shaded area. *$P \leqslant 0.05$ compared to baseline using a paired t test. $^{\dagger}P \leqslant 0.05$ compared to 3×10^{-4} M pinacidil using a paired t test.

ventricular fibrillation could not occur (Adaikan *et al.*, 1992). In rat isolated hearts, the antifibrillatory effect of tedisamil was limited to reducing the duration of ventricular fibrillation and had no influence on the incidence of ventricular fibrillation elicited by regional ischaemia and reperfusion (Tsuchihashi & Curtis, 1991). The results in the present study may suggest that blockade of more than one type of K^+ channel may be more effective in mediating antiarrhythmic activity. An additive or synergistic effect might exist between K^+ channel subtypes under the influence of certain compounds as suggested by the findings of Bril *et al.* (1993) who observed that the combination of tedisamil with E-4031 in the anaesthetized rat exerted a greater antifibrillatory effect than with tedisamil alone.

The inhibition of the ATP-regulated potassium channel may contribute to the antifibrillatory action of tedisamil in the pinacidil-treated hypoxic/reoxygenated heart. In the present experimental model, activation of the K_{ATP} channel by pinacidil serves an important role in the initiation of ventricular fibrillation (Chi *et al.*, 1993; Fagbemi *et al.*, 1993). Pinacidil selectively enhances the K_{ATP} current (Arena & Kass, 1989) and shortens the action potential duration, thus facilitating re-entry in myocardial tissue (Di Diego & Antzelevitch, 1993; Coromilas *et al.*, 1994). Hypoxia and reoxygenation lead to the development of an appropriate substrate for re-entrant arrhythmias facilitated further by a decrease in myocardial cellular ATP content which potentiates the action of pinacidil on the ventricular ATP-regulated potassium channel (Chi *et al.*, 1993). Inside-out patch clamp studies from rat ventricular cells demonstrate that tedisamil (20 μM) significantly decreased K_{ATP} channel activity (Faivre & Bril, 1992). Bril *et al.* (1993) observed that tedisamil and E-4031 increased the QTc more during ischaemia than during the pre-ischaemic period, suggesting that tedisamil and E-4031 may have an effect on a current involved during acute ischaemia, such as the K_{ATP} current. The ability of tedisamil to reverse the pinacidil-induced negative inotropic effect in rabbit isolated atrial tissue further supports our hypothesis that tedisamil inhibits the K_{ATP} channel in myocardial tissue (Figure 9).

The chemical defibrillatory effect of tedisamil was demonstrated in non-ischaemic rabbit isolated hearts in which ventricular fibrillation was induced by electrical stimulation (Figure 7). Tedisamil restored normal sinus rhythm under conditions in which the myocardial tissue was perfused under normoxic conditions. Thus, one would assume that cellular ATP content was normal and that the K_{ATP}-dependent channel would be closed (Kakei *et al.*, 1985). Our observation is consistent with the ability of tedisamil to terminate ventricular fibrillation in rat isolated hearts (Tsuchihashi & Curtis, 1991). In the latter studies, tedisamil (3 μM) reduced the duration of VF in regional ischaemic/reperfused hearts, but was unable to prevent the induction of VF. Chemical defibrillation in this model had been observed with other compounds possessing Class III activity (Friedrichs *et al.*, 1993; 1994). The mode and kinetics of action of tedisamil in the conversion of VF is different from that of ibutilide and clofilium. The frequency of the fibrillatory waves decreased immediately upon exposure of the heart to tedisamil and slowed progressively over time until VF was converted to normal sinus rhythm. The antiarrhythmic action of tedisamil in the normoxic heart may be related to its ability to inhibit the two potassium currents responsible for cardiac action potential repolarization under normoxic conditions, i.e. the transient outward current (I_{to}) (Dukes & Morad, 1989) and the delayed rectifier current (I_K) (Dukes *et al.*, 1990). ATP-regulated potassium channels are present in cardiac muscle cells (Noma, 1993), and would be closed and non-functional under conditions of normoxic perfusion thus making unimportant any action of tedisamil upon the $I_{K_{ATP}}$. However, we cannot exclude the possibility that partial sodium block by tedisamil might also contribute to threshold elevation, thereby slowing intramyocardial conduction. In contrast to other studies, tedisamil at 3 μM significantly increased the ventricular excitation threshold and prolonged the P-R interval at 1, 3 and 10 μM, suggesting an action of the drug upon

other ion channels (Figure 4b and c). There have been reports of sodium channel modulation by tedisamil. In single rat ventricular myocytes, the suppression of the sodium current by tedisamil occurred only at a concentration greater than 20 μM (Dukes & Morad, 1989; Dukes *et al.*, 1990).

Both positive and negative inotropic actions of tedisamil have been reported in *in vivo* and *in vitro* investigations as well as an improvement in cardiac function during myocardial ischaemia. These effects of tedisamil on cardiac function, however, were attributed primarily to its bradycardic action and subsequent favourable influence on the oxygen supply/demand balance in the ischaemic hearts (Grohs *et al.*, 1989; Duchosal & Opie, 1992; Raberger *et al.*, 1992). The bradycardic effect of tedisamil (under normoxia) was not observed in our investigation since the heart was paced throughout the experimental protocol (Table 2). Therefore, the antifibrillatory effect of tedisamil is due to its direct electrophysiological action, independent of any influence on the cardiac function and/or the extent of pathophysiological conditions. An increase in arterial resistance has been observed with other K^+ channel antagonists. Studies (Bray & Quast, 1992; Kreye *et al.*, 1992) indicate that tedisamil and glibenclamide directly modulate mechanical tension in rat and rabbit isolated vascular smooth muscle by affecting K^+ channels. An increase of blood pressure or vascular resistance has been observed with tedisamil experimentally *in vivo* as well as clinically (Beatch *et al.*, 1991; Mitrovic *et al.*, 1992; Thormann *et al.*, 1993).

In conclusion, tedisamil possesses an effective antifibrillatory and chemical defibrillatory action in two experimental models. The effects are independent of its potential bradycardic action and influence on cardiac function. The Class III antiarrhythmic activity, i.e., increase of refractoriness, and prevention and/or termination of re-entry appear to be the primary mechanisms for its antifibrillatory effects, although effects on the other channels including sodium and calcium cannot be entirely excluded. The nature of the experimental model indicates that blockade of the ATP-regulated potassium channel is important in mediating the electrophysiologic effects of tedisamil. However, the inhibition of the I_{to} and the I_k may likewise contribute to the beneficial effects. Tedisamil may be unique when compared to other Class III antiarrhythmic agents (E-4031 (Sanguinetti & Jurkiewicz, 1990) and Dofetilide (Carmeliet, 1992b)) that selectively block I_{Kr} current. Additional studies in more elaborate *in vivo* models are needed to determine fully its potential in the prevention of lethal arrhythmias.

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