Block of the Rapid Component of the Delayed Rectifier Potassium Current by the Prokinetic Agent Cisapride Underlies Drug-Related Lengthening of the QT Interval

Benoit Drolet, MSc; Majed Khalifa, PhD; Pascal Daleau, PhD; Bettina A. Hamelin, PharmD; Jacques Turgeon, PhD

Background—Lengthening of the QT interval and torsades de pointes resulting in cardiac arrests and deaths have been noticed during treatment with cisapride, a newly developed gastrointestinal prokinetic agent. The rapid (I_Kr) and slow (I_Ks) components of the delayed rectifier current (I_K) are candidate ionic currents to explain cisapride-related toxicity because of their role in repolarization of cardiac ventricular myocytes. Our objectives were to (1) characterize effects of cisapride on two major time-dependent outward potassium currents involved in the repolarization of cardiac ventricular myocytes, I_Kr and I_Ks, and (2) determine action potential–prolonging effects of cisapride on isolated hearts.

Methods and Results—A first set of experiments was performed in isolated guinea pig ventricular myocytes with the whole-cell configuration of the patch-clamp technique. Cells were held at −40 mV while time-dependent outward currents were elicited by depolarizing pulses lasting either 250 ms (I_K250) or 5000 ms (I_K5000). Effects of cisapride on the I_Kr component were assessed by measurement of time-dependent activating currents elicited by short pulses (250 ms; I_K250) to low depolarizing potentials (−20, −10, and 0 mV). Time-dependent activating currents elicited by long pulses (5000 ms; I_K5000) to positive potentials (+>30 mV) were recorded to assess effects of the drug on the I_Kr component. A second set of experiments was conducted in isolated guinea pig hearts buffer-perfused in the Langendorff mode to assess effects of the drug on monophasic action potential duration measured at 90% repolarization (MAPD90). Hearts were exposed to cisapride 100 nmol/L at decremental pacing cycle lengths of 250, 225, 200, 175, and 150 ms to determine reverse frequency-dependent effects of the drug. Overall, 112 myocytes were exposed to seven concentrations of cisapride (10 nmol/L to 10 μmol/L). Cisapride inhibited I_Kr, the major time-dependent outward current elicited by short pulses (I_K250) to low depolarizing potentials, in a concentration-dependent manner with an IC50 of 15 nmol/L (therapeutic levels, 50 to 200 nmol/L). Conversely, block of I_Kr by the drug was less potent (estimated IC50 >10 μmol/L). In isolated hearts (n=9 experiments), cisapride 100 nmol/L increased MAPD90 by 23±3 ms (P<.05) at a basic cycle length of 250 ms but by only 7±1 ms (P<.05) at a basic cycle length of 150 ms.

Conclusions—Block of I_Kr gives an explanation to lengthening of cardiac repolarization observed in isolated guinea pig hearts. Potent block of I_Kr is also likely to underlie prolongation of the QT interval observed in patients receiving clinically recommended doses of cisapride as well as severe cardiac toxicity (torsades de pointes) observed in patients with increased plasma concentrations of the drug. (Circulation. 1998;97:204-210.)

Key Words: electrophysiology ■ cisapride ■ torsade de pointes

The newly developed prokinetic agent cisapride promotes motility throughout the length of the gastrointestinal tract by increasing the release of acetylcholine from postganglionic nerve endings of the myenteric plexus.1,2 Consequently, the drug is widely used for reflux esophagitis, functional dyspepsia, gastroparesis, and more recently, for chronic constipation and irritable bowel syndrome.2 The most common adverse effects during cisapride therapy are relatively benign, such as transient abdominal cramping, borborygmi, and diarrhea.1 However, inappropriate lengthening of the QT interval and induction of major cardiac rhythm disturbances, such as polymorphic ventricular tachycardia (torsades de pointes), have been observed in some patients.4-8 Although some of these episodes have occurred at high doses of cisapride, several cases of torsades de pointes and sudden deaths have been seen unexpectedly in patients, including children, receiving clinically recommended doses of the drug.5,7

The study of the electrophysiological mechanism(s) responsible for the development of torsades de pointes is an area of extensive investigation. Experimental studies and clinical ob-

Received May 30, 1997; revision received September 4, 1997; accepted September 25, 1997.
From Quebec Heart Institute, Laval Hospital, Faculty of Pharmacy (B.D., M.K., B.A.H., J.T.) and Faculty of Medicine (P.D., J.T.), Laval University, Ste-Foy, Quebec, Canada, G1V 4G5.
Correspondence to Jacques Turgeon, PhD, Centre de recherche, Hôpital Laval, 2725 chemin Ste-Foy, Ste-Foy, Québec, Canada, G1V 4G5.
E-mail phajtu@hermes.ulaval.ca
© 1998 American Heart Association, Inc.
servations suggest that an abnormal repolarization due to block of outward repolarizing currents or to an increase in inward depolarizing calcium or sodium currents could be the cause of this phenomenon.10 These assumptions are supported by the recent linkage of candidate genes for cardiac potassium and sodium channels with genetically inherited forms of the long-QT syndrome.11–15 It is also believed that electrical intracardiac abnormalities resulting in early afterdepolarizations could cause triggered activity and torsades de pointes.16–18 Predisposing factors to the acquired forms of torsades de pointes include slow heart rate, hypomagnesemia, and hypokalemia.10 However, recent studies have also indicated that treatment with class I and class III antiarrhythmic agents, nonselecting histamine H1 receptor antagonists, macrolide antibiotics, and antifungal agents may predispose patients to proarhythmic events.19,20

Potassium currents responsible for limiting cardiac action potential duration vary depending on species and cell types. In guinea pig, dog, and human ventricular myocytes, the delayed rectifier current (I_K) is a major outward potassium current responsible for termination of the action potential plateau phase.21–23 In these species, I_K includes both a rapidly activating component (I_Kr) and a slowly activating component (I_Ks).23–25 Although I_Kr and I_Ks exhibit interspecies differences in their microscopic constant characteristics, macroscopic characteristics of I_K are preserved across species.23–26 I_K is usually described as a small current that activates rapidly (relative to I_Kr). The current exhibits voltage-dependent fast inactivation, resulting in a decrease in peak I_Kr activating current at potentials positive to 0 mV.27

Recent studies using rabbit Purkinje fibers have demonstrated that cisapride prolongs cardiac repolarization and induces early afterdepolarizations.28 Lengthening of cardiac repolarization was concentration-dependent (10 μmol/L to 100 μmol/L) and exhibited reverse frequency–dependence characteristics.28 These investigators demonstrated that cisapride exerts typical class III antiarrhythmic drug properties, thus explaining the lengthening of cardiac repolarization observed in humans during treatment with the drug.4–9 Conversely, the mechanism of action, ie, the modulation of specific ionic current(s) involved in these effects, has not been investigated yet. Therefore, the objectives of our study were (1) to characterize the effects of cisapride on two major potassium currents involved in repolarization of cardiac ventricular myocytes, namely I_Kr and I_Ks, using the whole-cell configuration of the patch-clamp technique and (2) to determine action potential–prolonging effects of cisapride on isolated hearts using monophasic action potential duration determined at 90% (MAPD90) repolarization as an index of cardiac repolarization.

**Methods**

Experiments were performed in accordance with institutional guidelines of Laval University on animal use in research. Animals were housed and maintained in compliance with the Guide to the Care and Use of Experimental Animals of the Canadian Council on Animal Care.

**Patch-Clamp Experiments**

**Cell Preparation and Solutions**

Experiments were performed on single ventricular myocytes obtained from adult guinea pig hearts by use of an enzymatic dissociation technique. All solutions used during the cell isolation procedure were oxygenated and maintained at 37°C. The hearts were mounted on a Langendorff apparatus and retroperfused for 5 minutes with solution A containing (in mmol/L) NaCl 132, KCl 4.8, MgCl2 1.2, HEPES 10, glucose 5, and CaCl2 1.8; pH was adjusted to 7.45 with NaOH. The hearts were then rinsed for 2 minutes with a calcium-free solution (solution B) containing (in mmol/L) NaCl 132, KCl 4.8, MgCl2 1.2, HEPES 10, and glucose 5; pH was adjusted to 7.45 with NaOH. At the end of this period, perfusion with a low-sodium/high-potassium HEPES-buffered solution (solution C, in mmol/L: NaCl 29, KCl 4.8, potassium glutamate 128, MgCl2 1.2, HEPES 10, and glucose 5; pH was adjusted to 7.45 with KOH) containing collagenase (final concentration, 300 U/mL; Boehringer) was started and continued until the system pressure dropped to 15 mm Hg (~15 minutes). Hearts were then perfused for 3 minutes with a solution (collagenase-free) made of a mixture of solution C and solution A (85:15) containing 0.3 mmol/L CaCl2. Hearts were finally perfused with a solution made of 60% solution C and 40% solution A containing 0.75 mmol/L CaCl2. At this point, the ventricles were cut down and minced slightly. After filtration through 200-μm nylon mesh, the dispersed cells were resuspended in solution A and maintained at 30°C before use.

The external solution used to superfuse cells during the recording of currents contained (in mmol/L) NaCl 145, KCl 4, MgCl2 1, HEPES 10, and glucose 5. Nisolindpine (Bayer Leverkusen) 0.2 μmol/L was added to eliminate the slow calcium inward current, and CaCl2 was omitted in the extracellular solution to shift I_Kr activation to positive potentials.29 The pipette solution contained (in mmol/L) MgCl2 2, CaCl2 1, EGTA 11, MgATP 5, KATP 5, and HEPES 10. The pH was adjusted to 7.2 with KOH, and the final potassium concentration was fixed at 505 mmol/L with KCl. Cisapride solutions of 10, 30, 100, and 300 μmol/L and 1, 3, and 10 μmol/L were prepared daily by dissolving required amounts of the hydrochloride salt of cisapride in DMSO. A constant volume of DMSO (100 μL; 0.1% vol/vol) was added to buffer solutions perfusing cells in the absence or the presence of various concentrations of cisapride.

**Electrophysiological Measurements**

A small aliquot of dissociated cells was placed in a 0.5-mL chamber mounted on the stage of an inverted microscope (model CK2, Olympus). Cells were allowed to adhere to the coverslip on the bottom of the chamber and were then superfused continuously with the external solution prewarmed at 30°C by a Peltier device (Medical System Corp). In our experiments, complete replacement of external solution contained in the chamber was achieved within 2 to 3 minutes when the superfusion rate was 2 mL/min. All currents were recorded in the whole-cell, voltage-clamp configuration of the patch-clamp technique using an Axopatch-1D amplifier (Axon Instruments Inc). Voltage-clamp command pulses were generated by a 12-bit digital-to-analog converter (model TL-1, Axon Instruments Inc) controlled by the PCLAMP software package (version 4.05b, Axon Instruments Inc). Heat-polished patch-clamp pipette electrodes were used (capillary glass from Radnoti Glass Technology Inc; Stareborg glass capillary tubing, 1.2 mm OD) that had a tip resistance of 3 to 5 MΩ (when filled with the pipette solution). Series resistance was compensated 50% to 80% to improve the fidelity of whole-cell voltage-clamp measurements.

**Protocols**

Rod-shaped cells with clear cross-striations, resting potential of at least −78 mV, and stable delayed rectifier (I_K) currents (as assessed during a baseline period of at least 4 minutes) were used. Effects of cisapride on the rapidly (I_Kr) and slowly (I_Ks) activating components of I_K were studied in cells held at −40 mV (to inactivate I_Kr) and depolarized by pulses lasting either 250 ms (I_Kr) or 5000 ms (I_Ks). Test potentials of depolarizing pulses varied between −20 and +50 mV for I_Kr but between 0 and +50 mV for I_Ks. I_Kr was measured by subtracting minimal amplitude of current measured during the first 20 ms of the pulse (outside the capacitive current) to the amplitude of activating current measured at the end of these pulses. After these pulses, cells were repolarized to −40 mV for at least 750 ms. In the presence of
Cisapride Is a Potent \( I_{Kr} \) Blocker

DMSO, the initial deactivation of \( I_K \) (tail current) was truncated in a time- and voltage-dependent manner (see “Results” section for discussion). This suggests the induction of another yet unidentified current by DMSO. More importantly, it invalidates measurement of tail current amplitudes as an assessment of the magnitude of \( I_K \) and/or \( I_{Kr} \).

**Data Storage and Analysis**

Currents were low-pass filtered at either 2 kHz (\( I_{K250} \)) or 100 Hz (\( I_{K5000} \)) by a four-pole Besel filter (\(-3 \text{ dB/octave}\)). Currents were sampled at 2 kHz (\( I_{K250} \)) and 400 Hz (\( I_{K5000} \)) by use of a 12-bit analog-to-digital converter (TL-1 DMA, Axon Instruments Inc) and stored on hard disk for subsequent analysis. Data are presented as mean±SEM. Concentration-dependent block of \( I_{K250} \) and \( I_{K5000} \) was tested by Hotelling’s \( T^2 \) test, and voltage dependency was tested by a conditional Hotelling’s \( T^2 \) test.\(^{30}\) In this analysis, a Shapiro-Wilk test was used to assess normality. The level of statistical significance was set at \( P<.05 \).

**Experiments With Buffer-Perfused, Isolated Hearts**

**Heart Isolation and Perfusion Technique**

Male Hartley guinea pigs (weight, 300 to 350 g; Charles River Laboratories, Montreal, Quebec, Canada) were anticoagulated by injection of heparin sodium (400 IU IP). Thirty minutes later, animals were killed by cervical dislocation, and the hearts were rapidly excised and immersed in cold (4°C) Krebs-Henseleit buffer containing (in mmol/L) glucose 11.2, KC1 4.7, CaCl2 1.2, NaHCO3 25, NaCl 118.5, MgSO4 2.5, and KH2PO4 1.2. This solution was continuously gassed with 95% oxygen plus 5% carbon dioxide (pH 7.4, 37°C) and filtered through a 5.0-μm cellulose acetate membrane to remove any particulate contaminants. Each heart was cannulated and retrogradely perfused via the aorta with the Krebs-Henseleit buffer at a constant pressure equivalent to 100 cm H2O. To permit rapid exchange in perfusion solutions, a double “Baker” heart perfusion system (Ealing Scientific Ltd) and two parallel liquid columns were used.

**Electrophysiological Measurements**

Hearts were electrically stimulated (programmable stimulator model 5325, Medtronic) at a basic cycle length of 250 ms (4 Hz) at three times threshold via two silver electrodes implanted in the epicardium of the left ventricle. A monophasic action potential catheter (Langendorff probe model 225, EP Technologies Inc) was introduced in the left ventricle through the mitral valve and securely positioned to record the action potential signal. Monophasic action potential signals were recorded on a computer for a duration of 3 seconds (digital sampling rate, 1 Hz) and stored on hard disk for analysis. Monophasic action potential duration was determined by analyzing all complete beats in the 3-second data file. These values were averaged by use of a routine designed specifically for this purpose and incorporated into the computer program (CVRP97 Cardiovascular Research Partner, Dayton System Enit). At least 10 complexes were used for each measurement.

**Protocols**

Hearts were perfused during a control period of 5 minutes to assess stability of the monophasic action potential signal. Monophasic action potential signals were recorded at a basic cycle length of 250 ms. Then, basic cycle length was changed to 225 ms, and the heart was paced for 1 minute before the monophasic action potential signal was recorded. The same procedure was repeated for cycle lengths of stimulation of 200, 175, and 150 ms. Thereafter, perfusion was performed with Krebs-Henseleit buffer containing cisapride 100 nmol/L for a period of 15 minutes at a basic cycle length of 250 ms. Monophasic action potential signals were recorded again at basic cycle lengths of 250, 225, 200, 175, and 150 ms. Perfusion with Krebs-Henseleit buffer containing no drug was then restarted to assess reversibility of drug effects.

\[ I_{K5000} \]

-50
-40
5000 msec
Baseline
Cisapride 100 nM

Figure 1. Time-dependent activating currents elicited by long pulses (5000 ms, \( I_{K5000} \)) to a high depolarizing potential (+50 mV) at baseline and in the presence of cisapride 100 nmol/L.

**Statistical Analysis**

Only hearts with reversal of cisapride effects on reperfusion with buffer containing no drug were included in the analysis. Data on the magnitude of cisapride effects were analyzed with a Student’s paired \( t \) test. Frequency-dependent effects were compared by conditional Hotelling’s \( T^2 \) test.\(^{30}\) All values are expressed as mean±SEM. Statistical significance was set at \( P<.05 \).

**Results**

The poor solubility of cisapride or its salts (tartrate or hydrochloride) in aqueous milieu at pH 7.4 (such as the extracellular solution used to perfuse isolated ventricular myocytes) limits its study in in vitro systems. Several strategies were then tested to constitute a stable aqueous solution of cisapride at pH 7.4. These attempts revealed that the more favorable approach in the conduct of our study was to dissolve the hydrochloride salt of cisapride in a limited amount of DMSO (100 μL) before dilution into the extracellular solution (final concentration of DMSO was 0.1% vol/vol). By doing so, we obtained solutions that were stable on the basis of visual inspection (no precipitation) for at least 8 hours at 37°C at a maximal concentration of 10 μmol/L.

However, before the assessment of the effects of cisapride on time-dependent outward potassium currents, it was mandatory to test the effects of DMSO on activating and tail currents of \( I_{K250} \) and \( I_{K5000} \). On examination of recordings obtained from cells exposed to DMSO 0.1% vol/vol, we noticed that tail currents of \( I_{K5000} \) and \( I_{K250} \) recorded at −40 mV after test pulses to low depolarizing potentials included a time-dependent inward current. Consequently, tail current amplitudes could not be measured to assess effects of cisapride on \( I_K \). We also noticed that amplitudes of \( I_{K250} \) and \( I_{K5000} \) activating currents could be reduced by DMSO. However, even higher concentrations of DMSO (0.5% vol/vol) did not alter the kinetics of activation of the elicited currents. This was confirmed by the absence of a time-dependent component in differential current obtained by subtracting normalized signals recorded at baseline and in the presence of DMSO for both \( I_{K250} \) and \( I_{K5000} \).

Fig 1 illustrates recordings of currents elicited by long pulses (5000 ms) at baseline and in the presence of cisapride 100 nmol/L. Activating current was elicited by a test pulse to +50 mV, and deactivating tail current was recorded after repolarization to −40 mV. Under these conditions, \( I_K \) represents the
major component of $I_{K5000}$ activating and tail currents. A small reduction in both activating and tail currents was observed in this cell on exposure to cisapride. A similar degree of inhibition was observed in 18 cells exposed to the same concentration of the drug (Fig 2). We estimated that IC$_{50}$ for inhibition of $I_{K5000}$ (mostly $I_K$) was $10^{-7}$ mol/L (Fig 2, inset). The exact IC$_{50}$ for block of $I_{K5000}$ could not be determined because of the poor solubility of cisapride at pH 7.4 for concentrations $>10^{-7}$ mol/L. Fig 3A illustrates the current/voltage relationship of $I_{K5000}$ measured at baseline and during exposure to cisapride 1 or 10 $\mu$mol/L (n=12 cells/concentration). Inhibition of $I_{K5000}$ activating current by cisapride was voltage-dependent at 1 and 10 $\mu$mol/L; greater inhibition was observed at low depolarizing potentials than at more positive potentials ($P<0.05$; Hotelling’s $T^2$ test; Fig 3B).

Fig 4 shows activating and tail currents of $I_{K}$ elicited by a 250-ms test pulse ($I_{K250}$) to 0 mV, followed by repolarization to $-40$ mV under control conditions (baseline) and in the presence of cisapride 100 $\mu$mol/L. Activating current was decreased $\approx60\%$ by cisapride. Fig 5 reports that block of $I_{K250}$ at low depolarizing potentials (0 mV) was reproducibly observed in 90 cells exposed to various concentrations of the drug (from 10 nM/L to 10 $\mu$mol/L). Interestingly, block of $I_{K250}$ was biphasic, suggesting two sites for inhibition: (1) decrease in current amplitude reached a maximum of 60% to 70% inhibition at 100 nM/L, (2) no further decrease in current amplitude was noticed even when concentrations were increased from 100 nM/L to 1 $\mu$mol/L, and (3) further block was observed only for concentrations $>1$ $\mu$mol/L. Data suggest that the component of $I_{K250}$ blocked by the lowest concentrations of cisapride corresponds to $I_{Kr}$, whereas block observed at the highest concentrations corresponds to inhibition of a small fraction of $I_K$ elicited by a test pulse to 0 mV. Estimated IC$_{50}$ for inhibition of the $I_{Kr}$ component was 15 nM/L (Fig 5, inset).

Block of $I_{K250}$ by cisapride was not only concentration-dependent but also voltage-dependent. Fig 6 illustrates the current/voltage relationship of block of $I_{K250}$ time-dependent activating current at 100 nM/L and 10 $\mu$mol/L. At a concentration of 100 nM/L, decrease in $I_{K250}$ was significant for test pulses to $-10$ and 0 mV ($P<0.05$ vs baseline), suggesting selective block of $I_{Kr}$ that exhibits rapid inactivation at potentials positive to 0 mV. The drug-resistant component of the time-dependent activating current elicited by pulses to positive membrane potentials corresponds mainly to $I_{Kr}$. At the highest concentration tested (10 $\mu$mol/L), not only the $I_{Kr}$ component but also the $I_K$ component were decreased by exposure of cells to cisapride.

Experiments performed in isolated guinea pig hearts (n=9 experiments) demonstrated that cisapride caused a significant increase in MAPD$_{90}$. A typical example of monophasic action potential recorded at baseline and during perfusion of cisapride 100 nM/L is illustrated in Fig 7A. Effects of cisapride were
time related and reversible on removal of the drug (Fig 7B). 
Proarrhythmic events were not recorded with this technique, although phase 3 depolarization resembling early afterdepolarizations could be noted (Fig 7A). Mean increases in MAPD$_{90}$ were $23 \pm 3$, $19 \pm 2$, $17 \pm 3$, $15 \pm 2$, and $7 \pm 1$ ms at basic cycle lengths of 250, 225, 200, 175, and 150 ms, respectively (Fig 8A). These results clearly indicate reverse frequency-dependent effects of the drug on cardiac repolarization. (Fig 8B).

**Discussion**

Results obtained in this study clearly indicate that cisapride possesses direct electrophysiological effects on major ionic currents involved in cardiac repolarization. Patch-clamp experiments in isolated guinea pig ventricular myocytes revealed selective block of $I_{Kr}$ over $I_{Ks}$. In addition, isolated heart experiments demonstrated effects of the drug on ventricular muscle. Our results provide an explanation for QT lengthening observed during treatment with cisapride at therapeutic plasma concentrations of the drug. Moreover, concentration-dependent block of $I_{Kr}$ by cisapride explains cardiac toxicity observed in patients after overdosing. In other patients, the unheralded nature of cisapride-induced cardiac toxicity may be explained, on one hand, by increased plasma concentrations of the drug (due to either physiologically reduced clearance of cisapride or inhibition of its metabolism by other drugs) or, on the other hand, by combined administration of action potential lengthening agents.

Many adult and pediatric case reports suggest a propensity of cisapride to cause arrhythmogenic effects during treatment with therapeutic doses or after overdose. In fact, from September 1993 to April 1996, the Food and Drug Administration’s Med Watch reporting program received reports of 34 patients in whom torsades de pointes and of 23 in whom prolonged QT interval developed while the patients were using cisapride. Interestingly, 32 of these 57 patients (56%) were also taking imidazole antifungal derivatives (ketoconazole, fluconazole, itraconazole, or metronidazole) or macrol-
ide antibiotics (erythromycin or clarithromycin). Drug metabolism studies have clearly demonstrated that CYP3A4 is the principal enzyme involved into the biotransformation of cisapride into its major metabolite, norcisapride. Imidazole derivatives as well as macrolide antibiotics are well-known inhibitors of the cytochrome P450 system and more specifically, of CYP3A4. Under conditions of decreased CYP3A4 activity, plasma concentrations of cisapride are expected to rise significantly. Indeed, a 10- to 20-fold increase in cisapride plasma concentrations was noticed during the coadministration of fluconazole and erythromycin.

Cardiac toxicity observed during overdosing or limited clearance of the drug supports the concept that arrhythmogenic effects of cisapride are concentration-dependent. Results obtained in our study are in agreement with this statement. In fact, we demonstrated a concentration-dependent decrease in two major currents involved in cardiac repolarization, namely, \( I_{Kr}\) and \( I_{Ks} \). Estimated IC\( _{50}\) for the inhibition of \( I_{Kr} \) (15 nmol/L) is lower than mean plasma concentration (100 nmol/L) usually measured in patients during the administration of usual doses of the drug (data on file, Janssen Pharmaceutica). Consequently, lengthening of cardiac repolarization is to be expected in most patients treated with the drug. Conversely, IC\( _{50}\) for block of \( I_{Ks} \) is \( >10 \) \( \mu \)mol/L and appears to be of no clinical relevance. However, during overdosing or limited elimination of cisapride, complete block of \( I_{Kr} \) or combined block of \( I_{Kr} \) and \( I_{Ks} \) (although minimal) could lead to excessive lengthening of cardiac repolarization and cardiac toxicity. It is interesting to note that macrolide antibiotics and imidazole antifungals have also been associated with lengthening of the QT interval. Several studies performed recently have demonstrated that cardiac potassium currents may also be the target of nonantiarrhythmic agents. This may give an explanation to the unheralded nature of proarrhythmic events observed in patients during combined drug therapy with or without antiarrhythmic agents.

Conclusions

Our study indicates that lengthening of cardiac repolarization is to be expected in patients during chronic treatment with therapeutic doses of cisapride. Block of the rapid component of the cardiac delayed rectifier current (\( I_{Ks}\)) and lengthening of \( \text{MAPD}_{90} \) were observed at clinically relevant concentrations of the drug. The degree of QT prolongation associated with cisapride therapy appears to depend on plasma concentrations of the drug, on the individual biotransformation capacity (CYP3A4 activity), and on the coadministration with other drugs causing pharmacokinetic (inhibition of CYP3A4) and/or pharmacodynamic (additional block of cardiac potassium currents) interactions.

Acknowledgments

This study was supported by the Medical Research Council of Canada (MT-11876) and by the Heart and Stroke Foundation of Canada (Québec). Benoit Drolet is the recipient of studentships from Merck Frosst Canada and the Fonds pour la Formation de Chercheurs et l’Aide à la Recherche (FCAR). Drs Daleau and Hamelin are recipients of scholarships from the Fonds de la Recherche en Santé du Québec. The authors also thank Michel Blouin and Lynn Atton for technical assistance and Serge Simard, MSc, for statistical analyses.

References

Cisapride Is a Potent $I_{Kr}$ Blocker


Block of the Rapid Component of the Delayed Rectifier Potassium Current by the Prokinetic Agent Cisapride Underlies Drug-Related Lengthening of the QT Interval
Benoit Drolet, Majed Khalifa, Pascal Daleau, Bettina A. Hamelin and Jacques Turgeon

Circulation. 1998;97:204-210
doi: 10.1161/01.CIR.97.2.204

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/97/2/204

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/