Sildenafil (Viagra) Prolongs Cardiac Repolarization by Blocking the Rapid Component of the Delayed Rectifier Potassium Current

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Background—Several cases of unexpected death have been reported with sildenafil in patients predisposed to ischemic cardiac events. Although acute episodes of ischemia could account for some of these deaths, we hypothesized that sildenafil may have unsuspected electrophysiological effects predisposing some patients to proarrhythmia.

Methods and Results—Studies were undertaken in 10 isolated guinea pig hearts that demonstrated prolongation of cardiac repolarization in a reverse use-dependent manner by sildenafil 30 μmol/L. Action potential duration increased 15% from baseline 117±3 to 134±2 ms with sildenafil during pacing at 250 ms cycle length, whereas a 6% increase from 99±2 to 105±2 ms was seen with pacing at 150 ms cycle length. Experiments in human ether-a-go-go–related gene (HERG)–transfected HEK293 cells (n=30) demonstrated concentration-dependent block of the rapid component (I_{Kr}) of the delayed rectifier potassium current: activating current was 50% decreased at 100 μmol/L. This effect was confirmed using HERG-transfected Chinese hamster ovary (CHO) cells, which exhibit no endogenous I_{Kr}-like current.

Conclusions—Sildenafil possesses direct cardiac electrophysiological effects similar to class III antiarrhythmic drugs. These effects are observed at concentrations that may be found in conditions of impaired drug elimination such as renal or hepatic insufficiency, during coadministration of another CYP3A substrate/inhibitor, or after drug overdose and offer a new potential explanation for sudden death during sildenafil treatment. (Circulation. 2000;102:275-277.)

Key Words: proarrhythmia ■ I_{Kr} blockers ■ sildenafil

The drug sildenafil citrate is a successful tool in the treatment of impotence through a selective inhibition of the phosphodiesterase V that inactivates cyclic guanine monophosphate (cGMP), the mediator of smooth muscle relaxation in the corpus cavernosum.1,2

As impotence is a common problem among patients with cardiac disease, sildenafil is increasingly prescribed by cardiologists.3 Several deaths have been reported in patients taking sildenafil, but it was generally assumed that they were related to an underlying disease (eg, ischemia) and not to a specific drug effect.3,4

We investigated whether unexpected electrophysiological effects of sildenafil on cardiac repolarization might provide an alternate explanation for an increased risk of sudden death. We therefore determined action potential–prolonging effects of sildenafil in isolated hearts and characterized the effects of the drug on I_{Kr} using the patch-clamp technique.

Methods

Experiments were performed in accordance with our institutional guidelines 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.

Experiments With Isolated Hearts

Experiments with isolated guinea pig hearts were performed as described previously.3 The hearts were perfused with Krebs-Henseleit buffer during a control period of 10 minutes, followed by 15 minutes with buffer containing 30 μmol/L of sildenafil dissolved in 100 μL of dimethylsulfoxide (DMSO). Perfusion with buffer containing no drug was then restarted during a 10-minute washout period. Monophasic action potentials from the left ventricle were recorded every 60 seconds for brief pacing cycle lengths (BCL) of 250, 200, and 150 ms.

Patch-Clamp Experiments

Experiments were performed on human ether-a-go-go–related gene (HERG)–transfected HEK293 cells. Preparation and harvesting of the HEK293 cells were done as described by Zhou et al.6 Membrane
currents were recorded in whole cell configuration using suction pipettes. The composition of superfusion and internal pipette solutions were described by Zhou et al. Sildenafil solutions of 1 to 100 μmol/L were prepared daily by dissolving required amounts of the drug in 100 μL of DMSO. The same volume of DMSO was added in baseline and washout buffer solutions. HERG gene was also transiently transfected in CHO cells as described by Bérube et al. Recordings of currents and composition of superfusion and internal pipette solutions were described by Bérube et al. All voltage-clamp experiments were performed at 22°C to 23°C.

**Statistical Analysis**

Data are presented as means±SEM. Isolated heart data on the magnitude of sildenafil effects were analyzed with a student’s paired t test. In the patch-clamp experiments, concentration-dependent block of HERG activating current was tested by Hotelling’s T² test. A P value <0.05 was considered statistically significant.

**Results**

**Experiments With Isolated Hearts**

Examples of monophasic action potentials recorded at baseline and during perfusion with sildenafil 30 μmol/L at a BCL of 250 ms are illustrated in Figure 1A. Experiments in isolated hearts (n=10) showed an increase in monophasic action potential duration measured at 90% repolarization (MAPD₉₀) during perfusion with sildenafil 30 μmol/L (Figure 1B). At a BCL of 250 ms, MAPD₉₀ increased from 117±3 ms at baseline to 134±2 ms after 15 minutes of drug perfusion (P<0.05), decreasing back to 126±4 ms after 10 minutes of washout (P<0.05 versus sildenafil). At the shortest BCL of 150 ms, MAPD₉₀ increased from 99±2 ms afterwashout buffer solutions. BCL indicates basic cycle length.

**Statistical Analysis**

Data are presented as means±SEM. Isolated heart data on the magnitude of sildenafil effects were analyzed with a student’s paired t test. In the patch-clamp experiments, concentration-dependent block of HERG activating current was tested by Hotelling’s T² test. A P value <0.05 was considered statistically significant.

**Results**

**Experiments With Isolated Hearts**

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**Patch-Clamp Experiments**

The mechanism of the action potential-prolonging effect of sildenafil was elucidated by the patch-clamp experiments in HEK293 and in CHO cells. Figure 2A shows activating and tail currents elicited by a 4-second step to +20 mV in a HERG-transfected HEK293 cell under control conditions, after 15 minutes of sildenafil 30 μmol/L, and after a 20-minute washout period. Panel B shows activating and tail currents elicited by a 1.25-second step to 0 mV in a HERG-transfected CHO cell under control conditions, after 15 minutes of sildenafil 30 μmol/L, and after a 20-minute washout period. Panel C shows HERG activating current amplitude, measured at +20 mV in HEK293 cells (n=30), normalized to control, plotted as a function of sildenafil concentration.
reduction of the activating current, and a $\sim$44% reduction of the tail current. Sildenafil 30 $\mu$mol/L had no effect on HERG channel activation, deactivation, or inactivation kinetics. In HERG-transfected HEK293 cells, block of activating currents was assessed with sildenafil concentrations ranging from 1 to 100 $\mu$mol/L and the data were fitted to the Hill equation, giving an estimated IC$_{50}$ of 100 $\mu$mol/L (Figure 2C).

Discussion
Our results indicate that sildenafil can prolong cardiac repolarization by blocking I$_{Kr}$. In fact, we have shown that sildenafil 30 $\mu$mol/L caused a clinically relevant 15% prolongation of cardiac repolarization, which is comparable with the effect of cisapride 100 $\mu$mol/L under the same conditions. It has been shown that I$_{Kr}$ block may lead to triggered ventricular arrhythmias and sudden death. These results provide a new potential explanation for sudden death during sildenafil treatment.

Inhibition of HERG current was demonstrated in both HEK293 and CHO cell lines. In HEK293 cells, the estimated IC$_{50}$ for I$_{Kr}$ was 100 $\mu$mol/L. Plasma concentrations of sildenafil after treatment with single doses of 25 to 100 mg are around 1 $\mu$mol/L. Because sildenafil is a strong lipophilic drug, relevant tissue concentrations are probably higher. However, based on our results, several-fold higher plasma concentrations than these encountered in clinical practice would be required before significant I$_{Kr}$ block occurred. Drug metabolism studies have demonstrated that CYP3As are the principal enzymes involved in the biotransformation of sildenafil. Thus, one could expect an important rise in sildenafil plasma levels when it is coadministered with CYP3A inhibitors (macrolides, imidazoles) or other CYP3A substrates (many cardiac drugs, such as calcium antagonists and statins). Indeed, a 20-fold increase in cisapride plasma concentrations (another inadvertent I$_{Kr}$ blocker that is a CYP3A4 substrate) was reported during coadministration with fluconazole and erythromycin.

The cardiovascular effects of sildenafil in randomized, controlled clinical trials were minor, although patients with underlying heart disease were generally excluded from these studies. From April 1998 through mid-November 1998, the FDA has been able to document 130 cases of death in US patients using sildenafil. Sixty-two percent of them died of cardiovascular events (mostly myocardial infarction or cardiac arrest), whereas the cause of death was unmentioned or unknown for 37% of patients. Therefore, care should be taken when prescribing sildenafil to patients with cardiac disease. Care should also be taken with patients at risk for impaired drug elimination and is further emphasized by these new findings. Because sildenafil can block I$_{Kr}$, caution is also needed during coadministration with other I$_{Kr}$ blockers such as class III drugs and other compounds such as erythromycin, antihistamines, and cisapride. Moreover, the present findings with sildenafil should also remind the whole concern of acquired long QT syndrome as a “drug-revealed” form of silent congenital long QT syndrome, observable under the effect of a growing list of drugs.

Conclusions
Sildenafil blocks I$_{Kr}$ and prolongs cardiac repolarization at concentrations that may be seen after drug overdose or in the presence of impaired drug elimination. Clinical attention to QT prolongation and triggered ventricular tachyarrhythmias is warranted in patients with hepatic or renal insufficiency or suffering from the long QT syndrome and in patients on multi-drug regimens.

Acknowledgments
Dr Geelen was the recipient of a postdoctoral fellowship from the Heart and Stroke Foundation of Canada. Benoit Drolet is the recipient of studentships from the Heart and Stroke Foundation of Canada and from the Fonds pour la Formation de Chercheurs et l’Aide à la Recherche (FCAR). Jimmy Rail was the recipient of a studentship from the Quebec Heart Institute. Dr Daleau is the recipient of a scholarship from the Fonds de la Recherche en Santé du Québec (FRSQ). Dr Rousseau is the recipient of a scholarship from the MRC/Canadian Hypertension Society. Dr Turgeon was the recipient of a scholarship from the Joseph C. Edwards Foundation. The authors also thank Michel Blouin and Lynn Atton for technical assistance. This work was presented in part at the 72nd Scientific Sessions of the American Heart Association, Atlanta, November 1999. Supported by Medical Research Council of Canada (MT-11876) (to J.T.) and Heart and Stroke Foundation of Quebec.

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_Circulation._ 2000;102:275-277
doi: 10.1161/01.CIR.102.3.275
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/102/3/275

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