Domperidone Should Not Be Considered a No-Risk Alternative to Cisapride in the Treatment of Gastrointestinal Motility Disorders

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Background—Several cases of QT prolongation and ventricular tachyarrhythmia have been reported with domperidone, a gastrokinetic and antiemetic agent available worldwide but still under investigation in the United States. Although electrolyte disturbances such as hypokalemia could account for some of these events, we hypothesized that domperidone may have unsuspected electrophysiological effects predisposing some patients to proarrhythmia.

Methods and Results—Studies were undertaken in 9 isolated guinea pig hearts, which demonstrated reverse use–dependent prolongation of cardiac repolarization by 100 nmol/L domperidone. Action potential duration increased 27% from baseline with domperidone (from 114±3 to 145±2 ms) during pacing at a cycle length of 250 ms, and a 9% increase (from 97±2 to 106±3 ms) was seen with pacing at a cycle length of 150 ms. Experiments in human ether-a-go-go–related gene (HERG)-transfected Chinese hamster ovary cells (n=32) demonstrated a concentration-dependent block of the rapid component (I_Kr) of the delayed rectifier potassium current. The tail current decreased by 50% at 162 nmol/L domperidone.

Conclusions—Domperidone possesses cardiac electrophysiological effects similar to those of cisapride and class III antiarrhythmic drugs. These effects are observed at clinically relevant concentrations of the drug. Therefore, domperidone should not be considered a no-risk alternative to cisapride, a drug that was recently withdrawn from the US market. (Circulation. 2000;102:1883-1885.)

Key Words: arrhythmia ■ ion channels ■ torsade de pointes ■ electrophysiology ■ long-QT syndrome

Domperidone (Motilium) has been marketed worldwide since 1978, but it is still under investigation in the United States. It is a unique compound that has both gastrokinetic and antiemetic activities. Chemically distinct from cisapride, domperidone is a peripheral dopamine-2-receptor antagonist that might seem to be an attractive, safer alternative to cisapride, a drug that was recently withdrawn from the US market due to drug-related proarrhythmic events.1–3 However, QT prolongation, life-threatening ventricular tachyarrhythmias, and even cardiac arrests have also been reported after the use of domperidone.4–11 It was generally assumed that these adverse effects were related to an underlying electrolytic disturbance, eg, hypokalemia, and not to a specific drug effect.5,7–9

We investigated whether unexpected electrophysiological effects of domperidone on cardiac repolarization might also provide an explanation for some of the observed proarrhythmic events. Therefore, we determined the action potential–prolonging effects of domperidone in isolated hearts and characterized the effects of the drug on a major cardiac potassium current (I_Kr) using the whole-cell 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.12 The hearts were perfused with Krebs-Henseleit buffer during a control period of 10 minutes; this was followed by 15 minutes of perfusion with buffer containing 100 nmol/L domperidone dissolved in 1 mL of DMSO. Perfusion with buffer containing no drug was then restarted during a 10-minute washout period. The same concentration of DMSO (0.1% v/v) was also present in baseline and washout buffer solutions. Monophasic action potentials from the left ventricle were recorded by a pressure-maintained catheter every 60 s for a 3-s period at basic pacing cycle lengths (BCL) of 250, 200, and 150 ms.

Patch-Clamp Experiments

Experiments were performed on HERG-transfected Chinese hamster ovary (CHO) cells. Preparation and harvesting of the CHO cells were done as described previously.13 Membrane currents were recorded in whole cell configuration using suction pipettes. The composition of the superfusion and internal pipette solutions was also described.
previously. Domperidone solutions of 30 nmol/L to 1 μmol/L were prepared daily by dissolving the required amounts of the drug in 100 μL of DMSO. The same concentration of DMSO (0.1% v/v) was also present in baseline and washout buffer solutions. All voltage-clamp experiments were performed at 22°C to 23°C.

Statistical Analysis
Data are presented as mean±SEM. The magnitude of domperidone effects for isolated heart data were analyzed with Student’s paired t test. In the patch-clamp experiments, the concentration-dependent block of the HERG tail current was tested by Hotelling’s T²-test. P<0.05 was considered statistically significant.

Results
Experiments With Isolated Hearts
Examples of monophasic action potentials recorded at baseline and during perfusion with 100 nmol/L domperidone at a BCL of 250 ms are illustrated in Figure 1A. Experiments in isolated hearts (n=9) showed an increase in monophasic action potential duration measured at 90% repolarization (MAPD₉₀) during perfusion with domperidone (Figure 1B). At a BCL of 250 ms, MAPD₉₀ increased from 114±3 ms at baseline to 145±2 ms after 15 minutes of drug perfusion (P<0.05); it then decreased back to 136±2 ms after 10 minutes of washout (P<0.05 versus domperidone). At a BCL of 200 ms, MAPD₉₀ increased from 110±2 ms at baseline to 130±3 ms after 15 minutes of drug perfusion (P<0.05); it decreased back to 118±3 ms after 10 minutes of washout (P<0.05 versus domperidone). Finally, at the shortest BCL of 150 ms, MAPD₉₀ increased from 97±2 ms at baseline to 106±3 ms after domperidone perfusion (P<0.05), and it returned to baseline levels after washout (99±4 ms). Thus, domperidone was associated with a 27% increase in MAPD₉₀ at the longest BCL and with a 9% increase at the shortest BCL. Such reverse use-dependent characteristics are typically seen with Iₖ blockers.

Patch-Clamp Experiments
The mechanism underlying the action potential–prolonging effects of domperidone was investigated by conducting patch-clamp experiments in CHO cells. Figure 2A shows the currents elicited in a HERG-transfected CHO cell perfused under control conditions (baseline), after 15 minutes of perfusion with 300 nmol/L domperidone, and after a 20-minute washout period. B, HERG tail current amplitude, measured at 20 mV in CHO cells (n=32) and normalized to control, plotted as a function of domperidone concentration.

Figure 1. A, Monophasic action potential signals recorded at baseline and after 15 minutes of 100 nmol/L domperidone at a BCL of 250 ms. B, Serial changes in MAPD₉₀ at BCLs of 250, 200, and 150 ms in hearts (n=9) sequentially perfused with buffer at baseline, 100 nmol/L domperidone, and washout buffer.

Figure 2. A, Activating and tail currents elicited by a 4-s step to 20 mV in a HERG-transfected CHO cell under control conditions (baseline), after 15 minutes of perfusion with 300 nmol/L domperidone, and after a 20-minute washout period. B, HERG tail current amplitude, measured at 20 mV in CHO cells (n=32) and normalized to control, plotted as a function of domperidone concentration.
Discussion

Our results indicate that domperidone can prolong cardiac repolarization in a reverse rate–dependent manner by blocking $I_{Kr}$. In fact, we showed that 100 nmol/L domperidone caused a significant prolongation of cardiac repolarization ($\approx 25\%$ to $30\%$). Excessive $I_{Kr}$ block may lead to triggered tachyarrhythmias and sudden death. These results provide a new explanation for QT prolongation and ventricular tachyarrhythmia during domperidone treatment.

An inhibition of the HERG current was demonstrated in CHO cells. The estimated IC$_{50}$ for $I_{Kr}$ was 162 nmol/L. Pharmacokinetic studies showed that the mean plasma concentration of domperidone in healthy subjects is 21 ng/mL (49 nmol/L) after 14 days of domperidone at a dose of 30 mg/d, which was similar to the mean plasma concentration of 18 ng/mL (42 nmol/L) observed after the first dose. However, the mean maximal concentration values achieved 30 minutes after 10 and 60 mg oral doses of domperidone were 23 and 80 ng/mL (54 and 188 nmol/L), respectively.

Therefore, a reduction of the $I_{Kr}$ current and delayed cardiac repolarization are expected to be seen in patients treated with the recommended doses of domperidone (10 to 20 mg TID/QID).

Similar electrophysiological properties have been extensively described recently with cisapride, another gastrokinetic drug. This drug had to be withdrawn from the US market due to unacceptable cardiac toxicity. Because cisapride was one of the overall most-prescribed drugs in the United States and definitely the most prescribed in its therapeutic class, its withdrawn will cause a rapid shift toward alternative therapies.

With both gastrokinetic and antiemetic activities, domperidone provides short-term relief of dyspepsia, diabetic gastroparesis, or nausea and vomiting associated with chemotherapy and antiparkinsonian drugs.

Unlike metoclopramide, another prokinetic dopamine-receptor antagonist, domperidone does not readily cross the blood-brain barrier, and reports of adverse effects on the central nervous system, such as dystonic reactions, are rare. Moreover, in the management of diabetic gastropathy, domperidone’s antiemetic activity distinguishes it from cisapride.

Because of its “apparent” favorable safety profile, domperidone might seem to be an appealing, safer alternative to cisapride. In view of the present findings and considering previous reports on domperidone cardiac toxicity, this should not be the case. Clinical attention should be directed toward QT prolongation and proarrhythmic events when domperidone is administered, as it was with cisapride. Because domperidone can block $I_{Kr}$, caution is also needed during coadministration with other $I_{Kr}$ blockers, like class III drugs and other compounds such as antimicrobials, antihistamines, and neuroleptics.

Domperidone should be one of the next compounds to add to the growing list of drugs associated with acquired long-QT syndrome.

Conclusions

Domperidone is a potent $I_{Kr}$ blocker. It prolongs cardiac repolarization at clinically relevant drug concentrations, and it should not be considered a no-risk alternative to cisapride. Therefore, clinical attention to QT prolongation and triggered ventricular tachyarrhythmias should be warranted when prescribing domperidone, particularly in patients with hepatic or renal insufficiency, in those who suffer from long-QT syndrome, and in patients on multidrug regimens.

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