Low safety index of domperidone: mechanism for increased odds ratio for sudden cardiac death

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Objective Domperidone is a dopamine antagonist with anti-nausea and anti-emetic activity. There have been several reports of sudden cardiac death (SCD) associated with the compound. Recently it was estimated to increase SCD nearly fourfold. I therefore tested domperidone for liability of cardiac repolarization disturbances (triangulation, reverse use dependence, instability and dispersion or TRiaD) and induction of arrhythmias.

Methods and results In Langendorff perfused rabbit hearts, domperidone significantly prolonged the action potential duration starting at 30 nM. It induced proarrhythmic TRiaD from 100 nM on. Since therapeutic free drug concentrations extend to 19 nM, the safety ratio for domperidone equals 100/19 = 5.25, i.e., far below the minimum safety ratio of 30. Hence, widespread use of domperidone cannot be without danger; especially since it is frequently used as an over the counter medication.

Conclusion In light of these new preclinical and of recent clinical warnings, domperidone should best be restricted to patients in whom its benefit is proven to justify the risks. Availability without prescription and advertising as an ‘innocent’ relief is incorrect and unsafe, and needs to be reconsidered.

Keywords Domperidone – QTc prolongation – torsade de pointes (TdP) – TRiaD.

INTRODUCTION

Domperidone (Motilium®, Touristil® in combination with cinnarizine) is a blocker of dopamine receptors used for suppression of nausea, vomiting and motion sickness1,2. A major advantage of domperidone is that its access to the central nervous system is very limited3. Although it is available in many countries without a doctor’s prescription, there exist nevertheless several reports dealing with cardiac side effects, including sudden death4. In a recent large-scale population-based epidemiological study, involving 1366 cases of ventricular arrhythmias and sudden cardiac death (SCD) and 14114 matched controls5, it was observed that the odds ratio for sudden death with domperidone was increased to 3.72 (95% confidence intervals of 1.72 to 8.08 ). For daily doses > 30 mg, the odds ratio increased to 11.4 (1.99 to 65.2).

An earlier preclinical study has claimed that the agent cannot be considered as a no-risk alternative to cisapride6. Their reason for considering domperidone as a potential risky agent, is based upon the fact that it blocks the rapid component of the cardiac delayed rectifier potassium (I_Kr) and can prolong the APD/QTc in isolated guinea pig heart. However, QTc prolongation is only a poor surrogate for TdP: there exist numerous drugs that prolong the APD/QTc without precipitating TdP7, TdPs also occur in the absence of QTc prolongation8 or even with QTc shortening9. Disturbances of repolarization, rather than the timing of repolarization, have been shown to be a more powerful predictor of proarrhythmia liability10.

I decided to test whether domperidone caused disturbances of repolarization, such as triangulation, reverse use dependence, instability and dispersion of the action potential (TRiaD) and arrhythmias in the isolated rabbit heart8,11.
METHODS

Preparation

Langendorff perfused rabbit hearts were used in the SCREENIT\textsuperscript{12} system. The investigation conforms to the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). Female albino rabbits of about 2.5 kg were stunned with a captivating bolt. The heart was perfused at a pressure of 80 cm with a buffer at 37°C of the following composition: NaCl 118, KCl 4, NaHCO\textsubscript{3} 22, MgCl\textsubscript{2} 1.1, NaH\textsubscript{2}PO\textsubscript{4} 0.4, CaCl\textsubscript{2} 1.8, dextrose 5, pyruvate 2, creatine 0.038 mM, 95%O\textsubscript{2} and ~5%CO\textsubscript{2}. CO\textsubscript{2} was adjusted by the computer to maintain pH at 7.35 ± 0.05.

The sectioned His bundle was stimulated at 1.5 threshold stimulation current. Septal and epicardial monophasic action potentials were recorded with 12 bits resolution and at 1 kHz, except for the conduction data which were obtained at 10 kHz. When automaticity and escape cycle length were >1000 ms, threshold stimulation current <300 μA, coronary perfusion >12 ml/min, ectopic rate <40 beats/10 min and the cardiac activation time <60 ms, then the preparation was stimulated until instability of the last 20 trains became less than 10 ms. Preparations not achieving these criteria were rejected.

Protocol

Every minute throughout the equilibration periods, a train of 30 action potentials at a cycle length of 1000 ms was recorded. Reverse use dependence was measured as the difference in APD\textsubscript{60} between the first 10 and last 20 APDs in a 30-beat train. APD\textsubscript{10}-APD\textsubscript{90} was determined as the length from the midpoint of the upstroke until 10, 20... 90% repolarization and the time from APD\textsubscript{10} to APD\textsubscript{90} was used as an estimate for triangulation of the action potential. Triangulation, reverse use dependence, instability or dispersion exceeding the 97.5 percentile of normal, was counted as a positive TRIaD score. Following a 10-minute baseline, the preparation was perfused with 5 consecutively tripled concentrations for 30 minutes. Each 30 min was composed of 15 min equilibration period, followed by a 15-min period for experimental determinations.

Chemicals

Domperidone was obtained from Sigma (Brussels, Belgium). A stock solution in dimethylsulfoxide (DMSO) was prepared daily and diluted in buffer to the required concentrations so that the DMSO concentration remained always below 0.1%. Therapeutic free drug plasma concentrations of domperidone are estimated to be in the 5-19 nM\textsuperscript{13}, but according to the manufacturer (McNeil, Johnson & Johnson): "In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 10-fold".

Statistical analysis

Data are presented as mean ± standard error (SE) and P-values < 0.05 were considered significant. Comparison between two means was done using Student’s t-test, while multiple means were compared with an analysis of variance. Electrophysiological deviations beyond the 2.5 to 97.5 percentile limits of drug-free mean were considered drug-induced. Instability of APD was computed using the best easy systematic\textsuperscript{14}: for the last 20 beats of 3 trains (60 action potentials in total), top and bottom quartiles were excluded (to minimize the bias induced by exceptionally long or short APDs) and the median and range were computed. Incidences of domperidone-induced EAD, TdP and TRIaD were tested for statistical significance with a Fisher’s exact test against 240 drug-free experiments (http://www.langsrud.com/fisher.htm).

RESULTS

Effects upon APD

At 10 nM domperidone non-significantly increased the APD\textsubscript{60} from 242 ± 10.2 ms to 260 ± 7 ms (figure 1), but at 30 nM the prolongation reached significance (269 ± 13.4; P < 0.05). At 1000 nM the APD\textsubscript{60} increased to 451 ± 35.4 ms (P < 0.001), but in 3 of the 6 experiments the prolongation no longer proceeded. Thus, the half maximum APD prolongation by domperidone must have been reached between 100 and 300 nM.

TRIaD

TRIaD incidences are summarized in figure 2. Domperidone (100 nM) induced significant triangulation (>23 ms) in 3 of 6 hearts (P<0.0001; figure 2). At 300 and 1000 nM of domperidone, the incidence increased to 5 of 6 hearts (P<10\textsuperscript{-6}).

Domperidone induced significant reverse use dependence at 300 nM (P<0.05) and 1000 nM (P<0.0001). The magnitude of reverse use dependence remained usually quite small having a median value of only 10.5 ms. Such small amount of reverse use dependence detected in a 30-beat train results from the very slow beat-by-beat rate of change of APD (figure 3): after a long diastolic interval (~10 s) at 1000 nM, the APD\textsubscript{60} had increased to 678 ms, thereafter it returned beat by beat in 3 minutes to its steady state value of 520 ms.
Instability and dispersion reached significant changes at 1000 nM domperidone in only a few experiments (figure 2). Such low incidence is unusual for agents that elicit such large disturbances of triangulation, but this too may be related to the slow kinetics of domperidone.

**Conduction**

Conduction was not slowed by domperidone up to 1000 nM.

**EADs**

EADs occurred in all 6 experiments ($P < 10^{-5}$). These started at 100 nM in one experiment, at 300 nM in two more and at 1000 nM in the 3 remaining experiments. The vast majority of these EADs occurred above 30% repolarization (plateau range) and were very small (< 10% of AP amplitude). In 3 of the experiments EADs also occurred between 40 and 60% repolarization (early in fast repolarization), where the amplitude sometimes exceeded 20% of the action potential amplitude. Finally, in 2 experiments EADs also occurred in the 60 to 80% repolarization where their amplitudes frequently became so large that they triggered ectopic beats and/or initiated TdP. In one of these latter two experiments, numerous runs of TdP developed. In total, 3 out of 6 preparations developed TdP ($P < 0.001$).
mathematically this can become problematic. These preclinical concerns are in line with numerous clinical studies.

In 2005, Strauss et al. demonstrated that in a study of several QTc-prolonging drugs, domperidone increased the odds ratio for SCD to 5.4 (2.2 to 12.7; 95% confidence intervals). These odds ratios were challenged by Johnson & Johnson sponsored authors, who, after careful analysis in a Saskatchewan Health database, reduced the odds ratio to 1.59 (1.28 to 2.04). In follow-up of the Strauss et al. study, the marketing authorization holder requested a more specific study focusing on domperidone. This new study by van Noord et al. found that domperidone significantly increases the odds ratio for sudden cardiac death to 3.72 (1.72 to 8.08) and to 11.4 (1.99 to 65.23) at oral doses > 30 mg.

Finally, cisapride has a free drug plasma concentration of 2.6 to 4.9 nM and first signs of TRIaD at 100 nM, i.e., a safety index of about 20. Thus, our results agree well with the experimental work and conclusion of Drolet et al. that ‘domperidone should not be considered a no-risk alternative to cisapride’. Furthermore, our results are also in agreement with the clinical report of Straus et al. showing a smaller odds ratio for cisapride (1.2; 0.4 to 3.5) than for domperidone (5.4; 2.2 to 12.7).

CONCLUSION

Domperidone has a narrow preclinical safety ratio (5.25) for cardiac repolarization disturbances and in epidemiological studies significantly increases the odds ratio for sudden cardiac death, also at normal therapeutic doses. Use of such an agent as an over the counter (OTC) drug therefore appears unwarranted.

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CONFLICT OF INTEREST

The author has done contract work for Johnson & Johnson.
REFERENCES