Effect of single doses of droperidol or haloperidol on QTc Interval

Emily Stephens, PharmD[1];Rachel Kahle, PharmD, BCPS[2,4]; Lindsey Ferraro, PharmD, BCPS[3,4]; Laura Schulz, RPH, BCPS[4]
[1]OhioHealth Mansfield Hospital, Mansfield, OH
[2]University of Findlay College of Pharmacy, Findlay, OH
[3]Ohio Northern University, Ada, OH
[4]Mercy Health St. Rita's Medical Center, Lima, OH

Abstract

Purpose: Droperidol and haloperidol are nonselective dopamine receptor blockers with clinical indications including postoperative nausea and vomiting and agitation. One signature side effect of both medications includes electrocardiogram (EKG) changes, such as QT prolongation. This may lead to torsades de pointes (TdP), a life-threatening arrhythmia.

Objectives: The primary objective of this study is to evaluate the change in the QTc interval following a single dose of droperidol or haloperidol.

Methods: This study entailed a retrospective chart review of inpatient medical records of adult patients who received a single dose of either droperidol or haloperidol. The primary outcome measure is the presence of QT prolongation following the administration of a single dose of droperidol or haloperidol.

Results: A total of 44 patients were included in the study. Patients were included in the study irrespective of their baseline QTc interval. QTc prolongation from baseline occurred in 52% of patients who received droperidol (13/25) and 79% of patients in the haloperidol group (15/19; p=0.113). As for patients who did not have prolonged QTc intervals at baseline, 9/15 patients (60%) in the droperidol group and 5/9 (56%) of patients in the haloperidol group experienced QTc after the study medication was administered (p=1).

Conclusions: There was no significant difference in the incidence of QTc prolongation following single doses of either droperidol or haloperidol. Future studies with larger sample sizes are needed to assess the effect of droperidol and haloperidol on QTc prolongation.

Keywords: haloperidol, droperidol, dopamine antagonists, electrocardiography, QT interval, torsades de pointes

Background

Droperidol and haloperidol are nonselective dopamine receptor blockers with clinical indications in the acute care setting, including postoperative nausea and vomiting and acute agitation.[1,2] Doses of droperidol for postoperative nausea and vomiting may range from 0.625 to 1.25 mg intravenous (IV) or intramuscular (IM), while initial doses for acute agitation should not exceed 2.5 mg IV or IM.[3] For acute agitation, additional 1.25 mg doses may be administered to achieve the desired effect.[1,3] Despite the recommended maximum initial dose of droperidol, providers may push to exceed this threshold, opting for doses greater than 2.5 mg.

Corresponding Author:
Rachel Kahle, PharmD, BCPS
Assistant Professor of Teaching in Pharmacy Practice
University of Findlay
1000 N Main St
Findlay, Ohio 45840-3653
Email: kohlsr@findlay.edu
ORCID: 0000-0001-7939-2913

Haloperidol dosing for postoperative nausea and vomiting are typically 0.5 to 2 mg IV or IM and doses for acute agitation may range from 0.5 to 10 mg IV, IM, or by mouth (PO).[2]

One signature side effect of both medications includes electrocardiogram (EKG) changes, such as QT prolongation.[1,2] The QT interval on a EKG represents ventricular systole; the QTc is the rate-corrected QT interval that normalizes the QT value to a standard heart rate of 60 beats per minute. This may lead to Torsades de Pointes (TdP), a life-threatening arrhythmia that can lead to sudden cardiac death.[1,2] The FDA issued a black box warning on droperidol in 2001 following a review of post-marketing reports detailing QT prolongation and subsequent development of TdP.[4] Following the implementation of the black box warning, the use of droperidol fell out of favor, despite it being an effective medication for nausea and vomiting. As a result of the black box warning and general fear of the potential risks associated with droperidol use, this medication seemingly disappeared from the United States (US) market following the implementation of the black box warning in 2001. Nuttall GA, et al conducted a retrospective study assessing low-dose droperidol and its risk for inducing QT prolongation and TdP in a general surgical population. There were 4,528 patients identified that had QT prolongation, TdP, or death within 48 hours of surgery.[5] A random sample of 150 patients from the time periods before and after the implementation of the black

box warning was analyzed to estimate droperidol use. Droperidol was used as an antiemetic in 12% of cases before the FDA black box warning and 0% after the black box warning due to unavailability. There was no difference in TdP incidence between time periods.

In 2019, manufacturers reintroduced droperidol to the market after reviewing the controversial data that influenced the black box warning. In reviewing the reports, researchers identified most incidences of QT prolongation and TdP that were presented to the FDA occurred following doses of droperidol greater than 25 mg.[4] A retrospective review by Jackson CW, et al. analyzed 277 case reports of cardiovascular adverse events related to droperidol that had been submitted to the FDA.[6] These reports were obtained under the Freedom of Information Act and had served as a basis for implementing the black box warning.[6] This review revealed 11 cases of TdP resulting in five deaths.[6] Four of the five deaths occurred outside of the US following IV doses of droperidol 600 mg for psychosis.[6] This review identified that there were multiple instances of duplicate case reports and 48.7% of the cases occurred outside of the US.[6]

The manufacturer's labeling for droperidol recommends that all patients undergo 12-lead EKG testing before receiving a dose of droperidol.[11] If the QTc interval is prolonged, then droperidol should not be administered.[1] The manufacturer defined prolonged QTc interval as QTc greater than 440 msec for males or 450 msec for females. Should the benefit of droperidol outweigh the potential risk for serious arrhythmias, EKG monitoring should be done for two to three hours after the dose.[1] The manufacturer's general recommendation regarding droperidol dosing is to initiate at low doses and adjust upward to effect.[1]

Droperidol was added to the Bon Secours Mercy Health formulary in 2020, with the requirement that an EKG be obtained prior to, during, or immediately after administration of doses >2.5 mg. For haloperidol, QT prolongation is listed as a significant adverse reaction to consider.[2] Despite being in the same pharmaceutical class and possessing a similar mechanism of action, haloperidol does not contain a black box warning like droperidol.[2] The purpose of the study is to assess the safety of droperidol and haloperidol with regard to QTc prolongation and evaluate the clinical relevance of the droperidol black box warning.

Objectives

The primary objective of the study was to evaluate if there was QTc prolongation following a single dose of droperidol or haloperidol. Secondary objectives included: to evaluate the QTc interval changes following administration of a single dose of droperidol or haloperidol, to evaluate the extent of QTc prolongation specifically in those patients who received single doses of droperidol greater than 2.5 mg, to assess the safety with regard to the presence of TdP, to identify Mercy Health - St. Rita's Medical Center's adherence to the EKG requirements stated in the formulary requirements for droperidol use and to assess the appropriateness of the current formulary requirements for droperidol use.

Method

This study was reviewed and exempted by the Mercy Health - St. Rita's Medical Center Institutional Review Board on October 31, 2023. This was a single-center, retrospective chart review of inpatient medical records. The study subjects included adult patients who received one dose of droperidol or haloperidol at Mercy Health - St. Rita's Medical Center between September 1, 2021 and August 31, 2023. Patients were excluded if they were less than 18 years old, received repeat doses of droperidol or haloperidol, had a permanent pacemaker, had right bundle branch block (RBBB) on EKG within 48 hours of the dose, had atrial fibrillation on EKG within 48 hours of the dose, on 3 or more scheduled QT-prolonging medications as defined in Table 1, potassium ≤ 3.5 mg/dL or magnesium ≤ 1.6 mg/dL prior to medication administration. In this study, we defined QTc prolongation as a QTc interval greater than 440 ms for males and greater than 450 ms for females. Patients were excluded if one or fewer EKGs were available in the electronic medical record as researchers would not be able to detect QTc interval changes without both a pre-dose and post-dose EKG. QTc prolongation was defined as a QTc interval greater than 440 ms for males and greater than 450 ms for females. QT-prolonging medications were obtained from CredibleMeds list of medications categorized as having known risk of TdP.[7] These medications were cross-referenced with medications on the institution's formulary, and the list utilized for evaluation is noted in Table 1.

Outcomes

The primary outcome measure is the presence of any QTc prolongation following the administration of a single dose of droperidol or haloperidol. Secondary outcome measures include median QTc interval change, presence of clinically relevant QTc prolongation, as defined as greater than 440 ms for males and greater than 450 ms for females, the presence of torsades de pointes within 48 hours of droperidol or haloperidol use, the presence of death within 24 hours of droperidol or haloperidol use, QTc interval change after doses of droperidol greater than 2.5 mg, and percentage of orders that are compliant with the Bon Secours Mercy Health System EKG requirements for droperidol

Statistics and Data Collection

In the absence of studies comparing QTc prolongation between droperidol and haloperidol, we assumed a 2% incidence of QTc prolongation after administration of a single dose of haloperidol. A minimum of 79 subjects per group were needed to detect a 15% difference in the incidence of QTc with a 90% power at a significance level of 0.05. Continuous data were tested for normality using QQ-plots and the

Shapiro-Wilk test. Normally distributed data were summarized as means and standard deviations and were analyzed using a two-sample t-test. Continuous data that failed the normality test were summarized as medians and interquartile ranges and were analyzed using the Mann-Whitney test. Count and percentage data were analyzed using the Chi-square or Fisher's Exact test. A logistics regression analysis test was conducted to identify factors that increase the risk of QTc prolongation. A p-value less than 0.05 was considered significant for all tests.

Table 1. QT-prolonging Medications

Medication Name
Amiodarone
Azithromycin
Chlorpromazine
Ciprofloxacin
Citalopram
Dofetilide
Donepezil
Dronedarone
Escitalopram
Flecainide
Fluconazole
Hydroxychloroquine
Ibutilide
Levofloxacin
Methadone
Moxifloxacin
Ondansetron
Procainamide
Sevoflurane
Sotalol

Results

A total of 851 patients were screened initially, with 807 patients being excluded for reasons detailed in Table 2. The most common reason for exclusion was lack of EKG in the electronic medical record with 172 patients excluded for having no EKG and 348 patients excluded for having only one EKG available. Repeat doses of either droperidol or haloperidol contributed to a high rate of patient exclusion with 191 excluded for this reason. The remaining 44 patients were included in the statistical analyses.

Table 2. Patient Screening

Reason for exclusion	n
17 years old or less	5
Repeat doses	191
Permanent pacemaker	7
Right bundle branch block	31
Atrial fibrillation with RVR	10
Serum potassium ≤ 3.5 mEq/L	41
Serum magnesium ≤ 1.6 mg/dL	2
No EKG	172
Only 1 EKG	348

Patients screened: n=851
Patients included: n=44
Patients excluded: n=807

Patient demographics of the study subjects are presented in Table 3. Baseline characteristics between the two groups were in general similar, aside from a higher pre-dose serum potassium concentration (median 4.3 mEq/L vs 3.9 mEq/L, p=0.008). Another baseline difference was that more patients received droperidol intravenously than haloperidol via the same route (68.0% droperidol vs 15.8% haloperidol, p=0.0008). The mean baseline QTc values were not significantly different between the droperidol and haloperidol groups (mean 441.8 ms vs 447.1 ms, p=0.528). Baseline QTc interval was prolonged in 20 of 44 patients (45.5%) and was not significantly different between the two groups (40% vs 52.6%, p=0.598).

Table 3. Patient Demographics and Baseline Characteristics

Characteristics		Droperidol (n=25)	Haloperidol (n=19)	p-value
Age (years), mean (SD)		52.44 (14.9)	57.74 (19.7)	0.335
Female, n (%)		14 (56)	11 (58)	1
Baseline QTc interval (ms), mean (SD)		441.8 (25.1)	447.1 (29.3)	0.528
Prolonged baseline QTc interval, n (%)		10 (40)	10 (52.6%)	0.598
Pre-dose K (mEq/L), median (IQR)		4.3 (4-4.5)	3.9 (3.8-4.1)	0.008
Pre-dose Mg (mg/dL), median (IQR)		2 (1.8-2.1)	2 (2-2.2)	0.360
Route, n (%)	Intramuscular	8 (32)	16 (84.2)	0.0008
	Intravenous	17 (68)	3 (15.8)	
Dose (mg), median (IQR)		1.25 (0.63-1.25)	5 (2-5)	n/a⁺

⁺Doses were not compared since the drugs are dosed differently.

The primary outcome of patients having QTc prolongation following a single dose of study medication occurred in 52% (132/254) of patients in the droperidol group and 79% (15/19) of patients in the haloperidol group (p=0.113). Development

of a clinically prolonged QTc interval, as previously defined as greater than 440 ms for males and greater than 450 ms for females, occurred in 12/25 of patients in the droperidol group (48%) and 11/19 patients in the haloperidol group (58%, p=0.729).

Table 4. Primary and Secondary Outcome Measures

Characteristics	Droperidol (n=25)	Haloperidol (n=19)	P-value
Post dose QTc (ms), mean (SD)	446.1 (34.5)	466.1 (34.4)	0.064
QTc change (ms), median (IQR)	4 (-12-22)	18 (1.5-32)	0.270
Patients with any prolongation in QTc, n (%)	13 (52.0)	15 (78.9)	0.113
Patients with clinically relevant prolongation in QTc, n (%)	12 (48.0)	11 (57.9)	0.729
Development of TdP	0	0	n/a[++]
Death	0	0	n/a[++]

[++]Comparisons were not performed.

Table 5. Univariate and Multivariate Logistic Regression of Factors that Increase the Risk of QTc Prolongation

Risk factor	Un-adjusted OR *(95% CI)	P-value
Drug: haloperidol vs droperidol	3.46 (0.94-14.9)	0.072
Sex: male vs female	5.77 (1.47-29.5)	0.019
Prolonged baseline QTc: yes vs no	0.22 (0.053-0.77)	0.023
Risk factor	**Adjusted OR *(95% CI)**	**p-value**
Sex: male vs female	5.57 (1.31-30.7)	0.029
Prolonged baseline QTc: yes vs no	0.22 (0.05-0.88)	0.038

[*]OR=Odds ratio; CI=confidence interval

A subgroup of patients who did not have a prolonged QTc interval at baseline were evaluated for QTc interval change. In the droperidol group, 60% of patients who did not have a prolonged QTc interval at baseline, experienced a clinically prolonged QTc interval (9/15). As for the haloperidol group, 56% of patients experienced QTc prolongation who did not previously have a prolonged QTc interval (5/9). The differences were not statistically significant. (p=1)

For the droperidol group, the route of administration did not statistically significantly affect QTc change with QTc prolongation occurring in 64.7% (11/17) and 25% (2/8) of patients who received droperidol via intravenous route versus intramuscular route, respectively (p=0.09684). Similarly, for the haloperidol group, there was no statistical difference in the percentage of patients who had QTc change between intravenous and intramuscular route with QTc prolongation occurring in 66.7% (2/3) and 81.3% (13/16), respectively (p=0.5304).

Logistic regression was performed to identify factors that increase the risk of QTC prolongation without taking its clinical significance into consideration. A univariate logistic regression showed that the type of drug patients received did not significantly increase the odds of QTc prolongation (haloperidol vs droperidol OR 3.46, CI 0.94-14.9, p=0.072). On the other hand, similar analysis showed that male patients had an increased odds of QTc prolongation (OR 5.77, CI 1.47-29.5, p=0.019) and those with prolonged baseline QTc had a decreased odds of QTc prolongation (OR 0.22, CI 0.053-0.77, p=0.023). The final multivariate model included sex and prolonged baseline QTc as risk factors. The adjusted odds ratios are shown in Table 5 and indicate a higher value in male patients after controlling for prolonged baseline QTc (OR 5.57, CI 1.31-30.7, p=0.029). In contrast, the OR was lower in patients with prolonged baseline QTc values after controlling for sex (OR 0.22, CI 0.05-0.88, p=0.038). When only clinically significant QTc prolongation was considered, univariate logistic regression showed the type of drug patients received did not significantly increase the odds of QTc prolongation (haloperidol vs droperidol OR 1.49, CI 0.450-5.03, p=0.516). Similarly, neither male sex (OR 2.18, CI 0.65-7.70, p=0.211) nor prolonged baseline QTc (OR 0.58, CI 0.172-1.92, p=0.379) increased the odds of clinically significant QTC prolongation after drug administration.

Discussion

The black box warning placed on droperidol in 2001 indicates that droperidol poses a significant risk for QTc prolongation and subsequent TdP and death.[4] When considering this advertised risk with the fact that droperidol and haloperidol exhibit similar mechanisms of action, the extent to which droperidol prolongs the QTc interval at clinically appropriate doses remains in question. Following the release of FDA reports that support the black box warning on droperidol, it was found that doses of droperidol used were greater than 100 mg and extended up to 600 mg.[6] Despite the irrelevance of such doses in today's practice, no studies have been conducted to assess the incidence of QTc prolongation of droperidol and how it may differ from haloperidol.

This retrospective study in patients who received single doses of droperidol or haloperidol did not demonstrate a statistical difference in the presence of QTc prolongation following administration of either study medication. While the results were not statistically significant, a greater percentage of patients who received haloperidol experienced any amount of

prolongation of the QTc interval and clinically relevant QTc prolongation when compared to those in the droperidol group. The subgroup analysis detailing patients who experienced QTc prolongation but did not have QTc prolongation at baseline demonstrated similar results between the two groups. It is apparent that the risk of QTc prolongation in either group is present; however, the extent of this prolongation remains unclear. The route of administration of the study medications and the effect on QTc interval was analyzed. While no conclusions may be drawn from the results of the current study, it did appear that droperidol had a greater incidence of QTc prolongation when given intravenously when compared to intramuscular administration.

This research study presented some limitations. Given the small sample size included in the study, the number of participants required to meet power was not met. An increased sample size would have allowed the researcher to better detect differences between the groups. Due to the small sample size within this study, the risk for type II error is amplified. This could lead to the assumption that there is no difference in the risk for QTc prolongation between droperidol and haloperidol, when in fact there is a difference. Another limitation was rooted in the single-center, retrospective study design. Had the study been prospective in nature, perhaps greater EKGs would have been obtained empirically to identify changes in QTc interval. Since 172 and 348 patients were excluded for having no EKG or only one EKG in the chart, respectively, this was a significant cause for inadequacy in the sample size, and potential for model overfitting. Additionally, if the study included more than one site, provider ordering patterns of study medication doses would have had greater variability. This may have led to the inclusion of droperidol doses greater than 2.5 mg which are acknowledged in the Mercy Health - St. Rita's Medical Center formulary requirements for use. As a result, the secondary outcomes relating to higher doses and this formulary requirement would have been explored further. While no droperidol with doses greater than 2.5 mg were included in the study, another limitation was the variable dose amounts and dose routes of the study medications. Droperidol doses ranged from 0.625 mg to 1.25 mg and haloperidol doses ranged from 1 mg to 5 mg. Additionally, both medications had varying rates of intravenous and intramuscular administrations. Such variability in dosing patterns poses a challenge when attempting to identify a relationship between the administration of droperidol and haloperidol on QTc prolongation. Luckily, zero patients developed TdP or died as a result of the study drugs. However, this makes an analysis of the related secondary outcome measures implausible.

Conclusion

Droperidol and haloperidol both pose a risk for QTc prolongation; however, the extent of such impact with clinically appropriate doses remains unclear. A larger study will be required in the future to adequately explore the impact of droperidol and haloperidol on QTc prolongation. Such a study should include doses of droperidol greater than 2.5 mg to identify if the manufacturer recommendation and Mercy Health - St. Rita's Medical Center formulary requirement for use remain relevant. Unfortunately, zero patients that were included in the study had received droperidol doses greater than 2.5 mg, so this study was unable to identify the effect of larger doses of droperidol on changes in QTc interval. Additionally, the appropriateness of the Mercy Health - St. Rita's Medical Center formulary requirement for droperidol use was not able to be assessed.

Acknowledgments: Eyob Adane, PhD (statistician)
Funding/Support: None
Disclaimer: The statements, opinions, and data contained in all publications are those of the authors.Conflict of Interest: None
Treatment of Human Subjects: IRB approval required and obtained (10/31/23)

References

1. Droperidol [package insert]. Lake Forest, IL: Hospira, Inc.; 2021
2. Haloperidol [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2020
3. Lexicomp Online, Lexi-Drugs, Hudson, OH: Wolters Kluwer Clinical Drug Information, Inc; 2024; Apr 18, 2024.
4. Kramer KJ. The Surprising Re-emergence of Droperidol. Anesth Prog. 2020 Sep 1;67(3):125-126. 10.2344/anpr-67-03-14.
5. Nuttall GA, Eckerman KM, Jacob KA, et al. Does low-dose droperidol administration increase the risk of drug-induced QT prolongation and torsade de pointes in the general surgical population? Anesthesiology. 2007;107(4):531-536.
6. Jackson CW, Sheehan AH, Reddan JG. Evidence-based review of the black-box warning for droperidol. Am J Health Syst Pharm. 2007 ;64(11):1174-1186
7. Woosley RL, Heise CW, Romero KA (2025). QTdrugs list, AZCERT, Inc.
8. https://www.crediblemeds.org . Accessed September 17, 2025.