SHORT COMMUNICATION

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Examination of Baseline Risk Factors for QTc Interval Prolongation in Patients Prescribed Intravenous Haloperidol

Andrew J. Muzyk,[1,2] *Amber Rayfield*,[3] *Jane Y. Revollo*,[4] *Heather Heinz*[4] and *Jane P. Gagliardi*[2,5]

1 Department of Pharmacy Practice, Campbell University College of Pharmacy and Health Sciences, Buies Creek, NC, USA
2 Department of Psychiatry & Behavioral Sciences, Duke University, Durham, NC, USA
3 Campbell University College of Pharmacy and Health Sciences, Buies Creek, NC, USA
4 University of North Carolina School of Pharmacy, Chapel Hill, NC, USA
5 Department of Medicine, Duke University, Durham, NC, USA

Abstract

Background: Intravenous haloperidol can increase the risk for corrected QT interval (QTc) prolongation, torsades de pointes (TdP) and sudden death. There are a number of risk factors reported in the literature for QTc prolongation and TdP with intravenous haloperidol.

Objective: The purpose of this study was to determine the prevalence of baseline risk factors for QTc prolongation and TdP in hospitalized medical inpatients prescribed intravenous haloperidol.

Methods: This is a retrospective cohort study of medically ill hospitalized inpatients prescribed intravenous haloperidol between 30 June 2007 and 1 January 2010. Records were ascertained for the presence of baseline risk factors for QTc prolongation and TdP.

Results: A total of 175 subjects were identified as receiving intravenous haloperidol during the study period. Mean age was 62.9 ± 19.1 years, and 48.6% of subjects were female. At baseline, 85.7% of subjects had ≥1 risk factor for QTc prolongation and TdP, with the majority of these subjects (58.0%) having between two and five risk factors. Of the total study sample, 74.9% had a baseline ECG; mean QTc value was 457 msec (± 40.8 msec). Greater than 50% of subjects had a sex-specific QTc value higher than the increased risk threshold of 450 msec in males or 460 msec in females at baseline. Following intravenous haloperidol administration, 46.9% of subjects had a follow-up ECG obtained within 24 hours. At the time of intravenous haloperidol administration, 93.1% of subjects had a potassium value available and 62.9% had a magnesium value. Approximately 30% of subjects had either a potassium or magnesium value below the normal laboratory range. Of the 175 subjects, 43.4% were taking ≥1 concomitant QTc prolongation medication at the time of intravenous haloperidol administration.

Conclusions: Consistent with previously published reports, patients in this study prescribed intravenous haloperidol had multiple risk factors, both modifiable and non-modifiable, at baseline for QTc prolongation and TdP. The modifiable risk factors may be important targets of interventions aimed at optimizing the safety of the use of intravenous haloperidol, while the non-modifiable risk factors may warrant closer scrutiny with consideration of alternative therapies and continuous monitoring.

Background

Haloperidol, a first-generation antipsychotic medication, is the preferred agent for the treatment of agitated delirium,[1,2] although systematic reviews of antipsychotics have found no difference in efficacy between haloperidol and newer second-generation antipsychotics.[3-7] Compared with other antipsychotics, haloperidol is often chosen in delirium because it is associated with fewer anticholinergic and sedating adverse effects as well as having fewer active metabolites.[8] Although not approved by the US FDA, intravenous administration of haloperidol is used most often due to better drug absorption, quicker onset of effect, reduced metabolite accumulation and decreased extrapyramidal symptoms compared with the intramuscular and oral preparations.[9] However, a recent FDA alert warning of corrected QT interval (QTc) prolongation, torsades de pointes (TdP) and sudden cardiac death with intravenous haloperidol raises concern about its safety.[10]

Published case reports and prospective studies demonstrate a direct association between administration of intravenous haloperidol and adverse cardiovascular events, particularly among medically ill patients being treated for post-operative delirium, patients with QTc-prolonging risk factors at baseline, and patients receiving high cumulative doses in a 24-hour period of time.[11-19] A review article further examining this issue, evaluating not only the literature but also the FDA's MedWatch programme, found that prescription of concomitant proarrhythmic agents, underlying cardiac disease and electrolyte imbalances were three commonly encountered risk factors in patients prescribed intravenous haloperidol who developed QTc prolongation or TdP.[20]

Despite these findings, there is no current consensus regarding the appropriate monitoring of patients prescribed intravenous haloperidol; although ECG monitoring is recommended, frequency of monitoring and parameters for discontinuing the medication have not been consistently specified.[1,2,10,21] Even haloperidol's prescribing information only provides a general recommendation that ECG monitoring should occur with the use of intravenous haloperidol.[21] There are also no consistent recommendations for baseline monitoring to identify additional risk factors, such as other non-cardiovascular medical illnesses, abnormal electrolytes and concomitant QTc-prolonging medications.[22-26]

Based on the risk factors reported in the literature for QTc prolongation and TdP with intravenous haloperidol, the purpose of this study is to determine the prevalence of these risk factors at baseline in hospitalized medical inpatients.

Methods

We performed a retrospective Drug Utilization Review (DUR) on injectable haloperidol. Patients were eligible for inclusion if they were ≥18 years of age and received intravenous haloperidol while hospitalized in one of two 32-bed standard-care medical units considered the 'home' units for general medicine patients at the study institution. We collected data from the time period of 30 June 2007–1 January 2010.

The following data were collected for each subject: age, sex, admitting diagnosis and length of hospital stay. If performed during the index hospitalization, results from baseline ECGs were recorded. Following administration of intravenous haloperidol, patients' charts were reviewed up to

24 hours to determine if a post-haloperidol ECG was recorded. In this institution, the ECG machines calculate QTc intervals using Bazett's formula[27] averaged over 12 leads; this method is considered accurate in the presence of underlying normal sinus rhythm.[28]

Patient charts were examined for non-modifiable risk factors, including cardiovascular (left ventricular dysfunction, left ventricular hypertrophy, ischaemia, slow heart rate less than 60 beats per minute, past history of syncope or a family history of sudden death at age <40 years[28]) and for other 'non-cardiovascular' conditions (alcohol dependence, liver disease, metabolic or endocrine disorders, medication overdose or central nervous system disorders).[24,29] The following additional modifiable risk factors for QTc prolongation, present at the time of intravenous haloperidol administration, were recorded: lowest potassium and magnesium values (if available) and concomitant proarrhythmic medications.[29] Concomitant proarrhythmic medications were identified based on the Arizona Cert – Center for Education and Research on Therapeutics website.[30]

The Investigational Review Board of Duke University Hospital granted an exemption to this study. No individually identifiable patient information was collected or maintained in study records.

Results

The initial DUR identified 306 individuals who were prescribed injectable haloperidol. Of these, 131 patients were excluded because they (i) were prescribed but did not receive intravenous haloperidol; or (ii) received intramuscular haloperidol. Table I contains the characteristics of the 175 subjects included in this study. A total of 172 subjects (98.3%) were admitted due to a variety of primary medical illnesses; the other three subjects (1.7%) were admitted to the medical unit with acute psychosis. When an indication was reported, delirium or altered mental status was most commonly chosen. There were no deaths during the index hospitalization.

A baseline ECG was available for 131 patients (74.9%), and the mean QTc value was 457 msec (± 40.8 msec). Greater than 50% of subjects had a QTc value higher than the sex-specific QTc threshold. Forty males had a QTc >450 msec and 27 females had a QTc >460 msec. Of the 131 subjects with ECGs, 16 patients (12.2%) had a baseline QTc ≥500 msec. Following intravenous haloperidol administration, 82 (46.9%) of the included subjects had a follow-up ECG obtained within 24 hours.

Overall, 163 subjects (93.1%) had a pre-intravenous haloperidol potassium value available for review. The mean potassium level was 3.7 mmol/L (± 0.5 mmol/L). Fifty (30.7%) of the

Table I. Subject characteristics

Characteristic	Number
Total number of subjects	175
Female sex [n (%)]	85 (48.6)
Age at admission [years; mean ± SD]	62.9 ± 19.1
Age at admission ≥65 years [n (%)]	80 (45.7)
Number of subjects with ≥1 risk factor[a] at baseline [n (%)]	150 (85.7)
Presence of 1 risk factor[a] at baseline	54 (36.0)
Presence of ≥2 to <5 risk factors[a] at baseline	87 (58.0)
Presence of ≥5 risk factors[a] at baseline	9 (6.0)
Number of subjects with ≥1 cardiovascular risk factor at baseline	80
Left ventricular dysfunction	29
Left ventricular hypertrophy	65
Ischaemia	14
Slow heart rate <60 bpm	10
Past history of syncope	9
Family history of sudden death (age <40 years)	1
Number of subjects with ≥1 non-cardiovascular risk factor at baseline	124
Alcohol dependence	34
Liver disease	30
Diabetes	43
Hypothyroidism	19
Overdose	4
Pituitary insufficiency	0
Obesity	48
CNS trauma/infection	4
Stroke	16
Length of hospital stay [days; mean ± SD]	16.3 ± 20.9

a Includes any risk factor (cardiovascular and non-cardiovascular) for QTc prolongation at baseline (see the Methods section for a detailed list of risk factors).

bpm = beats per minute; **QTc** = corrected QT interval.

subjects with baseline potassium values had subnormal values (normal range in our institution: 3.5–5.0 mmol/L). Eleven subjects (6.7%) had a potassium <3 mmol/L.

Overall, 110 subjects (62.9%) had a magnesium value available at the time of intravenous haloperidol administration. The mean magnesium level was 1.9 mg/dL (± 0.3 mg/dL). Of patients with baseline magnesium values, 29 (26.4%) subjects had a magnesium level below the normal accepted range of our hospital (normal range in our institution: 1.8–2.5 mg/dL). Twelve subjects (10.9%) had a magnesium value <1.6 mg/dL.

Of the total population of 175 subjects, 76 (43.4%) were taking one or more concomitant QTc-prolonging medication at the time of intravenous haloperidol administration.

Discussion

In this sample of 175 medical inpatients prescribed intravenous haloperidol for agitation, a high percentage (85.7%) had at least one risk factor for QTc prolongation. We identified a variety of both non-modifiable and modifiable risk factors. The modifiable risk factors may be important targets of interventions aimed at optimizing the safety of the use of intravenous haloperidol, while the non-modifiable risk factors may necessitate a clinical decision to use intravenous haloperidol with caution and continuous monitoring or to choose a different treatment.

As anticipated from the fact that these were medical inpatients, and consistent with prior literature, 85.7% of subjects had at least one risk factor for QTc prolongation and TdP, with the majority of these subjects (58.0%) having between two and five risk factors. This finding is alarming in light of a recent study in which 97% of patients who received intravenous haloperidol and developed QTc prolongation or TdP also had additional risk factors for these adverse outcomes.[20] This same study also found that cardiac disease was present in 47% of their subjects.[20] In our study, 80 of the 150 subjects with risk factors for QTc prolongation had at least one cardiovascular risk factor; left ventricular hypertrophy and left ventricular dysfunction were most common. Additionally, 124 of subjects had a 'non-cardiovascular' risk factor for QTc prolongation; obesity and diabetes were most reported. Liver disease, which could potentially impair the metabolism of haloperidol (which relies on cytochrome P450 enzymes),[14,21] was present in 30 subjects. Lastly, nearly 50% of the subjects were older than 65 years and approximately 50% were female; both are consistently reported risk factors for QTc prolongation and TdP.[26]

More than half of our sample had an available baseline ECG that demonstrated prolonged QTc before the administration of intravenous haloperidol; this is not unexpected given the variety of medical and cardiac co-morbidities seen among hospitalized medical patients at this institution, but is concerning with respect to cardiovascular risk. A QTc value ≥500 msec at baseline was seen in 12.2% of those patients with ECGs; this is considered a threshold value associated with increased TdP risk.[23] In a recent study, 60% of critical care pharmacists responding to a survey reported continuing intravenous haloperidol even though the QTc exceeded 500 msec, while 20% reported not even routinely measuring a QTc interval when this drug is prescribed.[31]

An ECG obtained within 24 hours following intravenous haloperidol administration occurred in approximately 50% of the subjects. Therefore, we are not able to provide useful information about QTc prolongation following intravenous haloperidol administration, nor was it the intent of this study. Traditionally, the greatest risk for TdP has been reported in previous studies among patients who received high cumulative doses of intravenous haloperidol within a short period of time, usually a 24-hour period, if not sooner.[17,32] However, low doses of haloperidol (doses ≥2 mg) have also been associated with QTc prolongation.[20,32,33]

In order to optimize patient safety with intravenous haloperidol administration at our institution, the computerized physician order set for intravenous haloperidol generates simultaneous orders for monitoring and safety. At the time of the initial order for intravenous haloperidol, the computerized physician order entry (CPOE) program generates a now order for an ECG, which is

ideally to be done prior to administration of the first intravenous haloperidol dose. Additionally, orders are generated and placed for daily early morning ECGs and daily morning laboratory assessment of serum potassium and magnesium levels for the 3 days following the order for the intravenous haloperidol. This is designed to facilitate recognition and correction of hypokalaemia and hypomagnesaemia, two common risk factors for QTc prolongation and TdP.[29] As evidenced by imperfect rates of baseline and follow-up ECG and electrolyte ascertainment, however, there are factors aside from CPOE programming that contribute to accomplishing monitoring. In this sample, patient-specific factors, including degree of agitation or willingness to undergo invasive (phlebotomy) or non-invasive (ECG) testing are important determinants of whether monitoring will be accomplished.

Although approximately 90% of subjects had baseline potassium values available at the time of intravenous haloperidol prescription, more than one-third of our sample did not have baseline magnesium levels. More importantly for assessing risk for QTc prolongation, approximately 30% of patients had a potassium or magnesium value below the normal laboratory value limit. These findings are similar to findings from a recent review that identified electrolyte imbalance as a risk factor in 40% of patients who developed QTc prolongation or TdP.[20] Additionally, studies of agitation in acutely psychotic patients have found a significant correlation between hypokalaemia and agitation. It is thereby possible that these patients may be at an increased risk for QTc prolongation and TdP if they receive an antipsychotic for tranquilization.[34,35] The findings from our study coupled with findings from the literature suggest that better recognition and correction of electrolyte imbalances may be an important first step in mitigating these adverse cardiac outcomes. Lastly, 43.4% of subjects were prescribed at least one concomitant QTc prolonging medication at the time of intravenous haloperidol administration; this is similar to findings from other literature.[20]

Our study has several limitations. The sample was selected from the routine medical care units, and not from step-down or intensive care unit populations who would have even greater risk of adverse outcomes from intravenous haloperidol administration. It is a retrospective cohort study with a small sample size, and prescribers chose medications based on clinical impressions that may have included risk assessment with respect to the QTc prolongation. For instance, providers may have selected intramuscular haloperidol for those patients who were at increased risk of cardiovascular events; further evaluation of the DUR might help to elucidate this question. Although all medical records were reviewed by two study authors (AM and JG) to ensure subjects met inclusion criteria, it is possible that patients may have been erroneously included or excluded from this study. Finally, although the CPOE order set was designed with the specific goal of accomplishing baseline ECG and electrolyte monitoring on all patients prescribed intravenous haloperidol, patient-specific factors, which may also impact the development of adverse cardiovascular outcomes and TdP, may have contributed to the less than 100% monitoring seen in our sample. Given the association between medical instability and agitation, our data may underrepresent the frequency of baseline risk factors and QTc prolongation.

Conclusions

Medically hospitalized inpatients may become agitated, and intravenous haloperidol is used with some regularity in this setting. Given the risks of intravenous haloperidol, with respect to QTc prolongation and TdP, reported in the literature, it is important to recognize risk factors for these adverse cardiovascular outcomes, particularly those that are modifiable, in order to optimize the safety of its use. Our data suggest that electrolytes and concomitant QTc-prolonging medications might be the most appropriate targets for intervention, and that prescribers may need education to increase awareness of the importance of identifying the presence of non-modifiable and modifiable risk factors at baseline before administering intravenous haloperidol. Prescribers must know the importance of ECG monitoring, both at baseline

and routinely following intravenous haloperidol administration, especially in those patients with multiple risk factors for QTc prolongation and TdP.

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Correspondence: Dr *Andrew J. Muzyk*, PharmD, Assistant Professor, Department of Pharmacy Practice, Campbell University College of Pharmacy and Health Sciences, P.O. Box 3089 – Pharmacy, Durham, NC 27710, USA.
E-mail: Andrew.Muzyk@duke.edu