SHORT COMMUNICATION

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A Computerized Physician Order Entry Set Designed to Improve Safety of Intravenous Haloperidol Utilization

A Retrospective Study in Agitated Hospitalized Patients

Andrew J. Muzyk,[1,2] *Sarah K. Rivelli*,[3,4] *Wei Jiang*,[3,4,5] *Heather Heinz*,[6] *Amber Rayfield*[1] and *Jane P. Gagliardi*[3,4]

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

Abstract

Background: Intravenous haloperidol can increase the risk for corrected QT (QTc) interval prolongation, torsades de pointes (TdP) and sudden death.

Objective: The purpose of this study was to examine the effects of implementation of a computerized physician order entry (CPOE) set on adherence to monitoring parameters, maximum and cumulative doses, and identification or mitigation of risk factors for QTc prolongation in patients prescribed intravenous haloperidol.

Methods: A retrospective cohort study of medically ill hospitalized inpatients prescribed intravenous haloperidol was conducted. Data were collected for two distinct 1-year time periods: the pre-CPOE set period (30 June 2007 through 30 June 2008) and the post-CPOE set period (1 January 2009 through 1 January 2010). The CPOE set was implemented on 1 October 2008.

Results: A total of 151 subjects were included; 84 subjects were in the pre-CPOE set group and 67 subjects were in the post-CPOE set group. Following CPOE set implementation, subjects in the post-CPOE group, compared with the pre-CPOE group, were more likely to receive a 24-hour cumulative dose of intravenous haloperidol <2 mg (Fisher's exact test; $p < 0.048$), have a baseline ECG (Fisher's exact test; $p = 0.045$), have a follow-up ECG within 24 hours of intravenous haloperidol administration (Fisher's exact test; $p = 0.009$) and have a magnesium value assessed at the time of intravenous haloperidol administration (Fisher's exact test; $p = 0.004$).

Conclusion: This study reports on the successful implementation of a CPOE set designed to improve the safety of intravenous haloperidol administration in medically ill patients.

Background

The risks of antipsychotic-induced corrected QT (QTc) prolongation and sudden cardiac death have been documented since the early 1960s.[1] Antipsychotics block the rapidly activating delayed rectifier potassium current, or IKr, which extends the period from ventricular depolarization to repolarization, thereby causing the QTc to be prolonged.[2,3] Prolongation of the QT interval can lead to torsades de pointes (TdP), a ventricular tachyarrhythmia associated with presyncope, syncope and sudden death.[4] All antipsychotics have the propensity to lengthen the QTc;[5-8] however, a 2007 US FDA alert highlighted increased risk of QTc prolongation, TdP and sudden cardiac death with the off-label intravenous administration of haloperidol and prompted specific language in haloperidol's package insert.[9] In response, haloperidol's package insert now recommends cautious use in patients with predisposing risk factors for QT-prolongation and recommends ECG monitoring.[10]

Published case reports and prospective studies have documented an association between intravenous administration of haloperidol and adverse cardiovascular events, particularly among medically ill patients being treated for post-operative delirium, patients with risk factors for QT prolongation at baseline, and patients receiving high cumulative doses in a relatively short period of time.[11-19] A review article examining this issue, evaluating not only the literature but also the FDA's MedWatch programme, drew similar conclusions.[20] At the same time, clinicians are faced with the difficulty of balancing the apparent effectiveness of haloperidol for agitated delirium, its place as a guideline-recommended treatment[21,22] and its potential risk for adverse cardiovascular events, especially when considering other factors such as the costs and labour required for continuous ECG monitoring.[20]

There is no current consensus regarding the appropriate monitoring of patients prescribed intravenous haloperidol. The FDA alert and haloperidol's package insert recommend ECG monitoring but do not specify frequency or thresholds for discontinuing the medication.[9,10] Major treatment guidelines range from recommending a baseline ECG[21] to recommending non-specific 'monitoring' when administering haloperidol.[22] The most recent summary of the evidence concludes with a recommendation for a baseline ECG for all patients and continuous ECG monitoring in those patients with a prolonged baseline QTc, other QT-prolonging risk factors or those receiving cumulative doses ≥2 mg.[20] Missing from the literature are clear recommendations for monitoring other contributors to TdP such as QTc measurement following intravenous haloperidol prescription, setting limits on cumulative haloperidol dose, checking and supplementing electrolytes (particularly potassium and magnesium), and identification and discontinuation, when possible, of other QTc-prolonging medications.

In an effort to optimize patient safety and physician education in response to the 2007 FDA warning, members of our institution's Pharmacy and Therapeutics Neurosciences Formulary Evaluation Team met with psychiatrists, cardiologists, electrophysiologists and hospital leadership to develop and implement a computerized physician order entry (CPOE) set for intravenous haloperidol. The order set automates baseline and daily ECG orders as well as daily magnesium and potassium monitoring in all patients prescribed intravenous haloperidol. The order set also prompts nursing staff to notify the responsible physician of any patient prescribed ≥20 mg in 12 hours or ≥35 mg in 24 hours of intravenous haloperidol, with a goal of avoiding total 24-hour cumulative doses ≥35 mg, which appears to be a threshold for risk of QTc prolongation based on existing literature. The 12-hour cut-off helps ensure that

nurses on both daytime and overnight shifts are expected to tally cumulative doses and to be mindful of possible risks. All intravenous haloperidol orders require the prescriber to enter an indication, with 'delirium' as the default, and all orders expire in 3 days unless renewed by a prescriber. The order set advises cautious use of intravenous haloperidol in patients with a QTc >500 msec, and provides a link to information on QTc-prolonging medications.

The purpose of this study is to examine the effects of implementation of the CPOE set on adherence to monitoring parameters, maximum and cumulative doses, and identification or mitigation of risk factors for QTc prolongation in patients prescribed intravenous haloperidol. The study was designed to test the null hypothesis that the cumulative daily dose of intravenous haloperidol, the frequency of baseline and routine ECG monitoring, and routine electrolyte monitoring would be the same before and after implementation of the CPOE set; the experimental hypothesis was that these parameters would differ after implementation of the CPOE set.

Methods

A Drug Utilization Review (DUR) search on injectable haloperidol was performed. Patients were eligible for inclusion if they were ≥18 years of age and received intravenous haloperidol while hospitalized on one of two 32-bed standard-care general medical units at our institution during the data collection period. Data was retrospectively collected for two distinct 1-year time periods: the pre-CPOE set period (30 June 2007 through 30 June 2008) and the post-CPOE set period (1 January 2009 through 1 January 2010). The CPOE set was implemented on 1 October 2008. We gave 2 months of period for the clinical practice system to familiarize with the order set prior to the post-CPOE set use data collection.

Age, sex and admitting diagnosis were collected for each patient. Data collected on intravenous haloperidol usage included average dose prescribed during the index hospitalization, total cumulative dose given in a 24-hour period and the maximum one-time highest dose. If an ECG was performed during the index hospitalization, QTc values were recorded. In the authors' institution, ECG machines calculate QTc intervals using Bazett's formula[23] averaged over 12 leads; this method is considered accurate in the presence of underlying normal sinus rhythm.[24] A potential ECG monitoring opportunity was defined as a 24-hour time period following intravenous haloperidol administration in which an ECG should be ordered based on the CPOE set; if multiple intravenous haloperidol doses were given in a short period of time then an ECG was needed within 24 hours following the last intravenous haloperidol administration. The lowest potassium and lowest magnesium values within 24 hours of intravenous haloperidol were recorded. The decision to include the lowest potassium and magnesium values was made because QTc prolongation is correlated with hypokalaemia and hypomagnesaemia, which are both modifiable contributors to risk.[2] Review of medication administration records was conducted to identify and record administration of other QTc-prolonging medications during the time of intravenous haloperidol prescription. QTc-prolonging medications were identified based on the Arizona Cert – Center for Education and Research on Therapeutics website.[25] Adherence to the recommendations reflected in the CPOE set was measured in both the pre- and post-CPOE set time periods.

Due to the small sample size, data analysis was performed mainly using descriptive statistics. Fisher's exact test was used to calculate p-values for categorical variables and a Student's t-test was used to compare means for normally distributed data. This study was granted an exemption by the Investigational Review Board of Duke University Hospital, and no protected health information was collected or maintained in study records.

Results

The initial DUR search identified 224 individuals who were prescribed injectable haloperidol during the two time periods. Of these, 73 patients were excluded because they (i) were prescribed but never received intravenous haloperidol; or (ii) intramuscular haloperidol was administered.

Table I. Subject characteristics

Measure	Pre-CPOE set	Post-CPOE set	p-Value
Number of subjects	84	67	NC
Female sex [n (%)]	47 (56.0)	31 (46.3)	0.255[a]
Age [y; mean ± SD]	62.5 ± 19.3	64.8 ± 18.7	0.466[b]
Age ≥65 years (% of subjects)	46.7	53.3	0.625[a]

a Indicates p-value calculated by Fisher's exact test.

b Indicates p-value calculated by Student's t-test.

CPOE = computerized physician order entry; **NC** = not calculated.

Overall, 84 subjects were included in the pre-CPOE set group and 67 subjects were included in the post-CPOE set group. Patient characteristics are described in table I. There were no significant differences in the characteristics of these two subject populations.

Table II shows information on intravenous haloperidol dosing in the two groups. The mean dose and total cumulative dose of intravenous haloperidol were not significantly different between the two groups. Fewer subjects in the post-CPOE group received a 24-hour cumulative dose of intravenous haloperidol ≥2 mg, and this was statistically significant (47.8% vs 64.3%, respectively; $p < 0.048$). Five subjects (6.0%) in the pre-CPOE set group received ≥20 mg of intravenous haloperidol in a 24-hour period compared with one subject (1.5%) in the post-CPOE set group.

The percentage of subjects with baseline ECGs was higher in the post-CPOE set period (80.6%) than the pre-CPOE set period (65.5%), and this difference was statistically significant ($p = 0.045$). Baseline QTc values were comparable across the two time periods (mean ± SD 453.8 ± 46.9 msec vs 468.2 ± 63.4 msec for pre- vs post-CPOE set subjects, respectively; $p = 0.379$).

Subjects in the post-CPOE set period were significantly more likely to have an ECG following intravenous haloperidol administration (61.2% vs 39.3% for the pre-CPOE set subjects; $p = 0.009$). A follow-up ECG was conducted within 24 hours following an intravenous haloperidol dose 25.2% of the time (58 out of 230 potential monitoring opportunities) in the pre-CPOE set group versus 58.5% of the time (76 out of 130 ECG potential monitoring opportunities) in the post-CPOE set group. The highest QTc values for subjects with ECGs available within 24 hours following intravenous haloperidol administration were similar at 468.1 ± 27.5 msec for the pre-CPOE set versus 465.8 ± 41.1 in the post-CPOE set group (Student's t-test; $p = 0.789$). Five subjects (6.0%) in the pre-CPOE set group were lacking a potassium value at the time of intravenous haloperidol administration compared with nine subjects (13.4%) in the post-CPOE set group; this was not statistically different. There was also no difference between groups in the proportion of subjects with a potassium value <3.5 mmol/L at the time of intravenous haloperidol prescription. In the pre-CPOE set group, 43 of 84 subjects (51.2%) had magnesium values available at the time of intravenous haloperidol administration; in the post-CPOE set group, 50 of 67 subjects (74.6%) had baseline magnesium values; this difference was statistically significant ($p = 0.004$). There was no significant difference between groups in the proportion of subjects with a magnesium value <1.8 mg/dL at the time of baseline ECG. Rates of concomitant QTc-prolonging medications were similar between groups at approximately 50%.

Table II. Intravenous haloperidol dosing information

Measure	Pre-CPOE set	Post-CPOE set	p-Value
Dose (mg; mean ± SD)	1.9 ± 1.3	1.9 ± 1.9	0.701[a]
Cumulative amount of haloperidol in 24-hour period (mg; mean ± SD)	4.8 ± 6.4	3.4 ± 5.6	0.166[a]
Number of subjects (%) with cumulative amount of haloperidol in 24-hour period ≥2 mg	54 (64.3)	32 (47.8)	0.048[b]

a Indicates p-value calculated by Student's t-test.

b Indicates p-value calculated by Fisher's exact test.

CPOE = computerized physician order entry.

Discussion

Optimizing patient safety through computerized provider order entry has been an important goal since its inception. Although haloperidol is not approved for intravenous administration, it is commonly used in the medical setting for the treatment of agitation; yet there are cardiovascular risks associated with its use, particularly concerning in medically ill patients. We endeavoured to utilize CPOE to improve the safety of intravenous haloperidol administration while educating providers at a tertiary care academic hospital.

In building the CPOE set, we identified four monitoring elements based on key modifiable contributors to QTc prolongation with intravenous haloperidol administration: (i) baseline and follow up ECGs; (ii) potassium and magnesium monitoring; (iii) limiting the total daily dose to <35 mg daily; and (iv) limiting QTc-prolonging medications by highlighting such information to providers.

Of the four elements, our data suggest that implementation of the CPOE set was associated with changes in three elements. Baseline and follow-up ECGs were more prevalent in the post-CPOE set era, although rates were still lower than anticipated. The CPOE set automates orders for baseline and follow-up ECGs, but other factors play a role in the implementation of orders, including patients' willingness to consent to an ECG, patients' level of agitation and feasibility of obtaining an ECG in a given clinical context. Thus, the degree of behavioural impairment that prompts a prescriber to order intravenous haloperidol in the first place may limit the feasibility of carrying out an ECG. Future interventions to improve adherence to the orders and improve rates of follow-up ECGs may be warranted, such as encouraging staff to repeatedly try to obtain the test. More subjects had magnesium values recorded at the time of intravenous haloperidol administration. Additionally, there was a significant decrease in the number of subjects receiving intravenous haloperidol ≥2 mg in a 24-hour period following CPOE set implementation. This is an encouraging finding since a recent evidence review found cumulative doses of intravenous haloperidol ≥2 mg to be one of the risk factors associated with increased risk for QTc prolongation and/or TdP.[20] Additionally, lower doses of haloperidol are recommended for the treatment of delirium in older persons,[21,26] and approximately 50% of our patient population was ≥65 years of age. Daily doses vary, but 10 mg of haloperidol is an average daily dose reported in the literature for the treatment of delirium.[20,27] Lastly, the CPOE set may have positively influenced the use of higher dose intravenous haloperidol, as evidenced by the reduction in the proportion of subjects receiving ≥20 mg in a 24-hour period.

It is not entirely surprising that a link to information regarding QTc-prolonging medications did not result in any decreased concomitant use of such agents. Ideally, a system would provide immediate feedback to the prescriber about any concomitant QTc-prolonging medications. Moreover, the phenomenon of 'alert fatigue' is a well-documented pitfall of CPOE systems, in which prescribers' response to alerts either results in annoyance, more worrying or apathy regarding the alerts generated in the system.[28] The data, therefore, do not clearly support a role for provision of such alerts in decreasing concomitant QTc-prolonging medications. The possibility remains that focused alerts reflecting the specific patient's actual medications and risk of QTc prolongation related to actual medication combinations, as opposed to only general alerts, may be more effective in changing provider behaviour and improving patient safety.

Identification of modifiable risk factors may be more important than baseline QT interval. Specifically, hypomagnesaemia and hypokalaemia are correctable risk factors for QTc prolongation and TdP. A recent review article on this topic found that electrolyte imbalance was reported in 40% of cases where intravenous haloperidol induced QTc prolongation and/or TdP.[20] However, in a survey of psychiatric and emergency department providers, basic metabolic panel or comprehensive metabolic panel, both of which include serum potassium levels, were considered part of 'medical clearance' among only 42% of emergency physicians and 77% of psychiatrists.[29] Other 'electrolytes', presumably including serum magnesium, were considered part of 'medical

clearance' among only 23% of emergency physicians and 51% of psychiatrists who responded to the survey.

In this sample, rates of baseline potassium measurement were high, an expected finding given the fact that the routinely ordered basic metabolic panel includes potassium. However, rates of baseline magnesium measurement were relatively low. The proportion of subjects having a baseline magnesium measurement at the time of intravenous haloperidol administration significantly increased following CPOE set implementation. Although this study was not designed to measure mortality or cardiovascular outcomes, minimizing the risk associated with intravenous haloperidol administration may be a factor to consider in determining policy regarding routine ascertainment of magnesium values. It is still not clear from the literature, or from the authors' experience, whether baseline magnesium should be measured uniformly in all patients prescribed intravenous haloperidol or to only a subset of patients with comorbid illness associated with hypomagnesaemia, such as chronic alcohol use.

Although encouraging (these results indicate an impact on prescribing and monitoring following the implementation of our CPOE set designed to enhance safety of intravenous haloperidol administration), this study has several limitations. It is a retrospective cohort and decisions to prescribe intravenous haloperidol were clinically based on information that may have included risk assessment with respect to the QTc prolongation. Additionally, the sample was limited to subjects hospitalized on general medicine floors who were prescribed intravenous haloperidol. Patients hospitalized on step-down or intensive care units in our institution have more acute medical illnesses, which would increase their risk of TdP. On the other hand, and the reason for their exclusion in this study, automatic supplementation protocols for potassium and magnesium are implemented in those patient care settings and may contribute to improved risk profiles for patients who become agitated and need intravenous haloperidol. In combination with the small sample size, the relatively judicious use of intravenous haloperidol prevented the examination of outcomes such as mortality or cardiovascular events. Larger studies are needed to explore the benefit of a CPOE set in reducing cardiovascular mortality associated with intravenous haloperidol use and to assess the cost effectiveness of CPOE set implementation.

Conclusions

This study reports on the successful implementation of a CPOE set designed to improve the safety of intravenous haloperidol administration, which is commonly used for the off-label treatment of agitation among medically ill and delirious patients. The findings from this study demonstrate that the use of a CPOE set improved a number of patient safety measures, important when prescribing intravenous haloperidol, such as ECG and electrolyte monitoring. Additionally, there was a reduction in the proportion of subjects who received intravenous haloperidol ≥2 mg in 24 hours. Rates of concomitantly-prescribed QTc-prolonging medications were unchanged following CPOE set implementation. Decision support or other mechanisms to help prescribers identify and minimize concomitant QTc-prolonging medications may be a beneficial strategy for future interventions aimed at optimizing the safety of intravenous haloperidol prescription.

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

