Pharmacogenomic Response of Haloperidol in Critically Ill Adults with Delirium

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ABSTRACT

Objective

To characterize the pharmacogenomic (PG) properties of low-dose haloperidol for delirium treatment of critically ill adults.

Design

Single-center, prospective cohort study.

Setting

A mixed ICU at an academic medical center.

Patients

Critically ill adults with delirium [Intensive Care Delirium Screening Checklist (ICDSC) score ≥ 4] admitted to the ICU ≥ 48 hours and administered low-dose IV haloperidol using an institutional treatment protocol [1mg IV q8h; increased by 0.5mg IV q8h daily if delirium persisted up to 2mg IV q8h].

Measurements and Main Results

Each patient was evaluated with the ICDSC every 8 hours by a trained nurse. The QTc interval was calculated daily from a 12-lead ECG. Serum haloperidol concentrations were collected before each morning dose on days two through six and analyzed using standard liquid chromatography-mass spectrometry techniques. At baseline, CYP2D6 and CYP3A4 genotypes were determined and patients were categorized as extensive (EM), intermediate (IM) or poor (PM) metabolizers. The 22 patients (age 67 [48,77] years; APACHE III 81[54,181]; CYP2D6 [EM=12, IM=7, PM=3], CYP3A [EM=18, IM=4]) received an average daily haloperidol dose of 3.5±1.8 mg. Serum trough haloperidol concentrations were not significantly associated with either the daily haloperidol dose administered ($p = 0.3$), daily presence of delirium ($p = 0.2$) or cumulative ICDSC score ($p = 0.4$). PM CYP2D6 status was associated with significantly higher haloperidol concentrations ($p = 0.017$); an association between CYP3A4 status and haloperidol concentrations was not found. No patient experience QTc interval prolongation (≥500ms).

Conclusions

This pilot study, the first to evaluate the pharmacogenomics properties of low-dose haloperidol in critically ill adults with delirium, suggests trough serum haloperidol are lower in patients with a CYP2D6 PM status but, overall, are not associated with the daily dose administered, delirium occurrence, or changes in delirium symptoms.

INTRODUCTION

Haloperidol is frequently administered at low (4 to 8 mg/day) or moderate (9-20 mg/day) dose to critically ill adults to either prevent or treat delirium despite evidence from randomized, controlled trials that it neither prevents or resolves delirium nor improves important outlines like mortality or post-ICU cognition [1-5]. The achievement of low, and potentially inadequate, serum haloperidol concentrations has been postulated as a reason why low-dose haloperidol failed to prevent delirium in the recent REDUCE trial [6]. However, none of the most recent haloperidol ICU delirium treatment trials published to date [3-5] included pharmacokinetic data and thus the pharmacodynamic response of low-moderate dose haloperidol for the treatment of delirium in critically ill adults remains unclear.

Haloperidol is metabolized through both the CYP2D6 and CYP3A4 isoenzyme systems [7]. CYP2D6 and CYP3A4 polymorphisms are common and the activity of each may be affected by critical illness and the administration of any medication that is metabolized by one or both of these pathways [8]. Pharmacogenomic variability may therefore be an important contributor to haloperidol's pharmacodynamic response in a critically ill adult with delirium however the pharmacogenomics of haloperidol in this setting has never been evaluated. Although the pharmacodynamic, -kinetic, and -genetic characteristics of very high-dose haloperidol has been evaluated in patients with major psychiatric disorders [9], these properties have not been evaluated in critically ill adults receiving low-dose haloperidol for the treatment of delirium [1,4]. This data is important for the design of haloperidol dosing interventions in future studies and may help ICU clinicians individualize haloperidol dosing regimens for patients with clinically important delirium symptoms where its use may be warranted [10].

We therefore sought to characterize the pharmacogenetic characteristics low-dose haloperidol in critically ill adults with delirium.

METHODS

Study Enrollment

This single-center prospective observational pilot study was conducted in the adult intensive care units Erasmus University Medical Centre, Rotterdam, NL. The study was approved by the Institutional Review Board and informed consent was obtained from each patient or their next-of-kin. Consecutive adults (≥ 18 yrs.) expected to be admitted to the ICU ≥ 48 hrs with delirium [Intensive Care Delirium Screening Checklist (ICDSC≥4) [11] and administered haloperidol according to a preexisting institutional delirium protocol were evaluated for study participation between October 2014 and April

2017. Exclusion criteria included: treatment with haloperidol in the 24 hours prior to ICU admission; ICDSC not evaluated due to coma or severe hearing loss; end stage liver failure; primary neurologic diagnosis; a history of severe dementia; history of parkinsonism and/or psychosis; a baseline QTc interval ≥ 450msec; concurrent use of a medication with the potential to induce CYP2A6 and/or CYP3A4 isoenzyme concentrations (i.e., bosentan, carbamazepine, efavirenz, etravirine, phenobarbital, phenytoin, nevirapine, rifabutin, lopinavir, ritonavir, rifampicin); acute alcohol withdrawal; pregnancy; or no informed consent.

Data Collection

The following baseline data was collected: gender, age, APACHE III score, Body Mass Index (BMI), serum blood urea nitrogen, ICDSC score, QTc interval (based on ECG evaluation) and CYP2D6 and CYP3A4 isoenzyme concentrations. The following daily data was collected: daily change in ICDSC score, dose of haloperidol administered, SOFA (Sequential Organ Failure Assessment score, QTc interval, use of medications used in the ICU and known to inhibit CYP2D6 (amiodarone, cimetidine, fluoxetine, metoclopramide, metoprolol, paroxetine, and propranolol) and/or CYP3A4 (alprazolam, amiodarone, aripiprazole, clozapine, diazepam, erythromycin, fluconazole, melatonin, midazolam, quetiapine, risperidone, verapamil, voriconazole, zolpidem, and zopiclone) activity [12,13].

Delirium screening (by the ICU bedside nurse using the ICDSC every 8 hours) and reduction efforts were well-established in all study ICUs [14,15]. The investigative team conducted regular spot-checks of nurse ICDSC assessments, offering additional training to nurses when required. The ICU delirium treatment protocol advocated the use of haloperidol when the bedside nurse identified delirium and the physician agreed with nurse's assessment. Haloperidol was initiated at 1mg IV q8h [0.5 mg IV q8h if age ≥ 80 years old; 2mg IV q8h if agitation present] within 12 hours of delirium detection. On a daily basis, if delirium was still present, each dose of IV haloperidol was increased by 0.5mg to a maximum of 2mg IV q8h.

Blood samples for haloperidol concentration determinations were drawn from an arterial line before the administration of each morning dose on days 2, 3, 4, 5, and 6 (end of study) or until haloperidol was stopped before day 6 due to protocol, patient death or ICU discharge. Each blood sample was immediately sent to the hospital pharmacy laboratory, centrifuged, and the serum was stored at -80ºC until haloperidol quantification using validated, FDA-approved, liquid chromatography-mass spectrometry methods [16]. All serum concentrations were corrected for the most recent haloperidol dose administered.

CYP3A4 and CYP2D6 patient genotyping was performed using a validated method by the clinical chemistry laboratory at the study center. For each isoenzyme, patients were classified according to the number of active enzyme alleles present: poor metabolizers

(PM; two defective alleles), intermediate metabolizers (IM, 2 decreased activity alleles or 1 active and 1 inactive allele), extensive metabolizers (EM) and ultra-rapid metabolizers (UM, gene duplication positive in absence of a CYP2D6 null allele).

Data Analysis

The following analyses were conducted: 1. efficacy- association between daily haloperidol dose administered and highest ICDSC score, 2. safety- association between daily haloperidol dose administered and QTc intervals ≥ 500msec. 3. association between daily haloperidol dose administered and daily haloperidol trough concentrations, 4. association between highest daily ISCDC score and daily haloperidol trough concentrations. 5. Haloperidol pharmacogenomics: a. CYP2D6: association between CYP2D6 metabolizer status and daily haloperidol trough concentration, b. CYP3A4: association between CYP2D6 metabolizer status and daily haloperidol trough concentration and c. Association between CYP2D6 (and CYP3A4), haloperidol dose, and serum haloperidol concentrations over time. Additional analysis were conducted to account for use of co-medications known to inhibit one or both isoenzymes.

A convenience sample of 20 patients was chosen for this study given its pilot nature and the lack of published ICU data to provide a standard deviation for any of the outcomes evaluated. Data was presented as percentages, median (IQR) or mean (SD). To compare the daily mean haloperidol dose and QTc interval, a Student's t-test was used. To investigate the association between haloperidol dose, CYP2D6 and CYP3A4 metabolizer status, and serum haloperidol concentrations, a linear mixed model was constructed with haloperidol serum concentrations as the outcome of interest and haloperidol dose, baseline metabolizer status, patient age, ICU day, and the daily SOFA score as other covariates. To investigate the association between serum haloperidol concentrations and the presence of delirium, we constructed a generalized linear mixed model. Two-sided p values <.05 were considered statistically significant. Outliers were excluded from analysis. All analyses were performed using R (additional packages: foreign, lme4, and rms; R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/).

RESULTS

Baseline characteristics

Twenty-two patients (55% male, median 67 [48,77] years old, BMI of 27 [18, 39] kg/m^2, APACHE III 81 [54,181], serum BUN 18±13 mmol/L) were enrolled. The primary reasons for ICU admission included: surgery (7, 32%), respiratory failure (3, 14%), sepsis (3, 14%) and vascular aneurysm (2, 9%). The median length of stay of ICU stay was 16.5 [2, 63] days. Eleven patients died (50%); six patients during the ICU stay, four after ICU discharge, and

one after transfer to another hospital. Thirteen patients (59%) completed the maximum six days of data collection.

Haloperidol dose outcomes

Average haloperidol dose, ICDSC score, SOFA score and QTc interval across each study day are presented in **Table 1**. The average daily dose of haloperidol administered was 3.5 ± 1.8 mg. The distribution of daily haloperidol doses is presented in **Figure 1**. The average day 2 (3.3 ± 1.7 mg) and day 4 (4.2 ± 2.9) administered haloperidol doses were not different (p = 0.28). The daily distribution of serum haloperidol concentrations per patient are presented in **Figure 2.** The average daily haloperidol concentration among the 81 drawn was 1.9 [0 to 62] µg/L. Among four patients, seven concentrations exceeded 10 µg/L. An association between daily haloperidol dose and the haloperidol serum concentration was not found after adjustment for ICU day, age and daily SOFA score (p = 0.30).

Table 1: Average haloperidol dose, ICDSC score, SOFA score and QTc interval across each study day.

Parameter	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Daily haloperidol dose (mg)	2.6 (1.9)	3.2 (1.9)	3.3 (1.7)	3.6 (1.5)	4.2 (2.9)	3.8 (1.5)	4.2 (1.8)
Daily ICDSC[B] score	3.8 (1.4)	5 (1.1)	4.7 (1.5)	4.9 (1.6)	4.3 (2.1)	4.5 (1.7)	4.5 (1.8)
SOFA[B] score	10 (3.1)	9 (3.8)	9.3 (4.3)	10 (5.1)	9.8 (5.1)	8.4 (5.1)	9.7 (5.3)
QTc interval (msec)	413 (34)	423 (33)	425 (27)	418 (23)	413 (20)	414 (36)	423 (36)

[A]Data presented at mean ± SD

[B]ICDSC = Intensive Care Delirium Screening Checklist, SOFA = Sequential Organ Function Assessment

An association between the haloperidol serum concentration and delirium severity was not found (p = 0.20). An association between the haloperidol serum concentration and cumulative ICDSC score was also not found after adjustment for ICU day, age and daily SOFA score (p = 0.4).

Among the 92 ECGs performed, the QTc interval ranged from 318 and 486 ms; none exceeded 500 ms. The average QTc interval was not different between day 1 (423 ± 33 ms) and day 5 (413 ± 20 ms) (p=0.48).

Pharmacogenomic outcomes

The CYP2D6 genotype analysis revealed: extensive metabolizers (EM) (12, 54%), intermediate metabolizers (IM) (7, 32%), and poor metabolizers (PM) (3, 14%). No ultrarapid metabolizers were detected. We found that CYP2D6 PM status was significantly associated with higher haloperidol concentrations (p = 0.017) (**Supplemental Digital Content Figure 1**). The CYP3A4 genotype analysis revealed: EM (18, 82%) and IM (4, 18%). No ultrarapid metabolizers or PMs were detected. The association between CYP3A4 me-

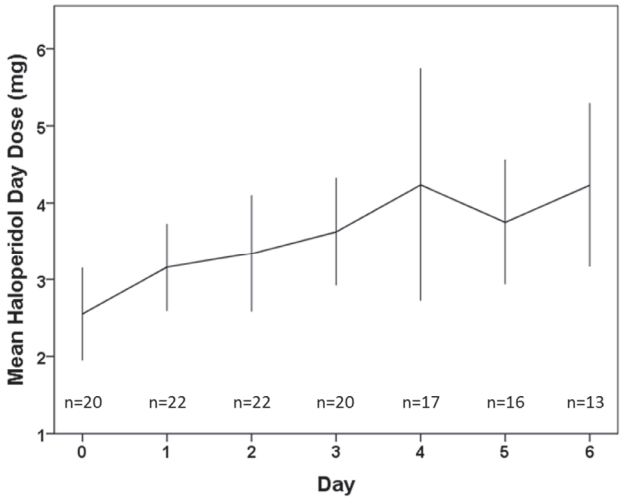


Figure 1: Average haloperidol dose administered each study day
Error Bars: 95% CI

tabolizer status and haloperidol serum concentrations was not found to be significant (p = 0.98) **(Supplemental Digital Content Figure 2).**

Most (18, 82%) patients received CYP2D6 inhibitors (often in combination) as follows: Metoprolol (10), amiodarone (8), metoclopramide (9) times. Many (13, 59%) received CYP3A4 inhibitors (also often in combination): erythromycin (5), amiodarone (7), voriconazole (2) and fluconazole (2).

The very high serum haloperidol concentrations (patient 1: 39.4; 54.4; 15.8; patient 2: 12.1; 10.1; patient 3: 59.9; patient 4: 62,2 µg/L) observed in four patients could be accounted for in two patients by a combination of new onset liver failure, CYP2D6/CYP3A4 genotype status and the administration of medications known to inhibit CYP2D6 and/or CYP3A4. In the other two patients, no clear reason for the high serum haloperidol concentrations observed were found and thus the two samples were excluded from the analysis. Theoretical explanations could be that samples were drawn from same central line haloperidol had recently been administrated through, or an error in the haloperidol measurement.

DISCUSSION

This single-center prospective observational pilot study is the first to evaluate the pharmacogenomics of low-dose haloperidol in critically ill adults with delirium. Scheduled IV haloperidol at dose of up 2mg q8h does not appear to affect delirium symptoms based

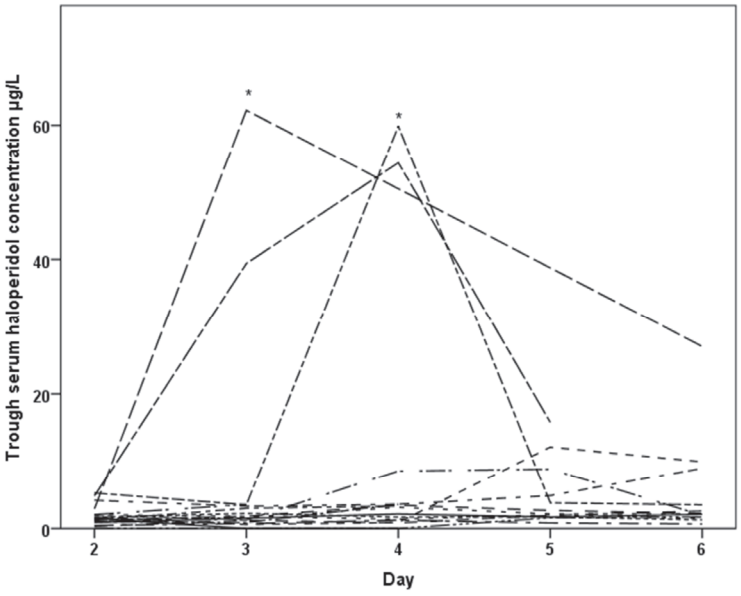


Figure 2: Observed haloperidol through concentrations per patient per day
Two outliers are marked with * and are excluded from statistical analyses

on the ICDSC assessments evaluated. The lack of relationship we observed measured serum haloperidol concentrations and the dose of haloperidol administered suggests that important factors other than age, severity of illness and day of administration account for the haloperidol concentration variability observed. While our results suggest CYP2D6 is an important contributor to this variability future research is required to define all factors that affect the pharmacodynamics response of low-dose haloperidol in critically ill adults.

While our data is consistent with a recent pharmacokinetic sub study from the REDUCE trial, it is important to recognize that the analysis in REDUCE trial was based on haloperidol use in patients without delirium and did not assess pharmacogenomic considerations like cytochrome P450 isoenzyme genotype [6]. It remains unclear if the lack of haloperidol benefit observed in our cohort is simply a result of the subtherapeutic haloperidol concentrations being achieved or reached or an intrinsic lack of response of delirium to haloperidol.

The results of two recent clinical trials in critically ill patients receiving low-dose haloperidol therapy have also reported a lack of effect on delirium resolution, and suggest – subtherapeutic serum concentrations are an important reason for a lack of effect [1,4]. However, the MIND trial [3], where haloperidol was administered at a dose of 15 mg/day, reported an average study day two serum haloperidol trough concentration of 4.5 [2.9,5.8] µg/L - nearly three-times the concentration we report – and also reported no

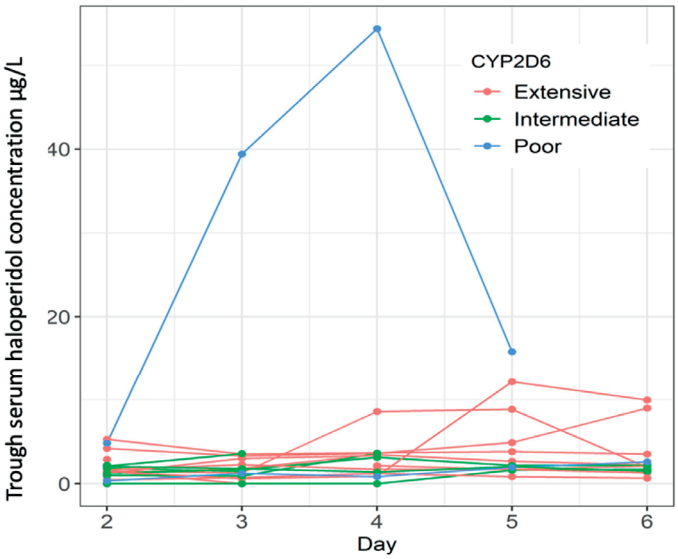
clinical benefit with haloperidol use. Importantly, with the recent MIND-USA trial finding even higher doses of IV haloperidol (20mg/day) not to be associated with improved delirium resolution or other clinical benefit, suggests that haloperidol has an intrinsic lack of effect on delirium [17].

Outside the ICU setting in patients with acute schizophrenia the therapeutic window for positive effects of haloperidol therapy has been reported to be in the range of 5.6 to 16.9 µg/L with a recommended target concentration of 10 of µg/L [9]. Whether the therapeutic haloperidol doses in schizophrenia patients compare with doses needed in an ICU-delirium remains unclear. A recent paediatric ICU study suggested, contrary to our study, that haloperidol is potentially effective but had higher risk for adverse events, despite low haloperidol plasma concentrations (0.005-0.085 mg/kg/d, equal to approximately 0.35 – 5.95 mg/day for an adult weighing seventy kilo) [18].

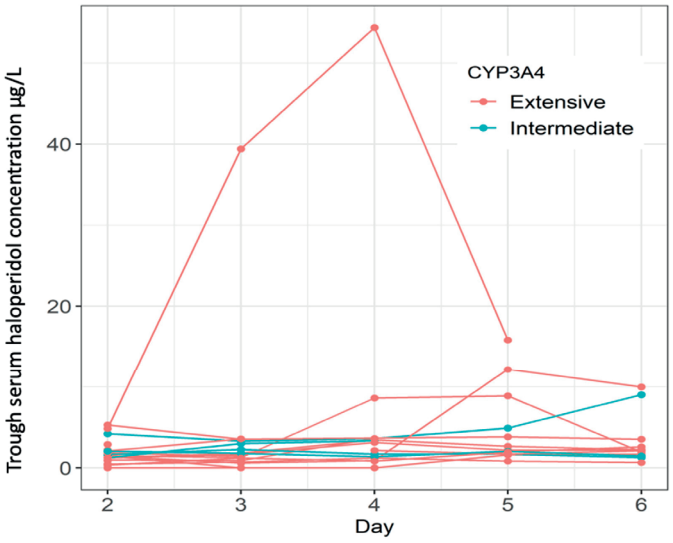
Our study has several limitations. Our analysis was neither controlled nor blinded. Although patients with factors that could influence the clinical, pharmacokinetic or genomic outcomes evaluated were excluded, the heterogenous nature of any ICU population like our population may have confounded the results we report. Our study was a pilot and considering the variability between patients we report; future investigations should focus on evaluating larger numbers of patients and at a greater range of haloperidol dose administration. Although we wanted to keep our analysis as pragmatic as possible, many patients received 1 or more medications known to affect haloperidol serum concentrations. Future studies on PK/PD of haloperidol in critically ill adults should aim to describes clearance, AUC. and distribution volume of haloperidol to test clinical efficacy. Furthermore, more extensive PK studies, e.g. on steady state kinetics and more extensive pharmacogenetics studies are clearly indicated. Finally, future studies may focus more on individual delirium symptoms rather than delirium either being present or absent, given the results of recent trials with haloperidol for ICU delirium.

CONCLUSIONS

This report represents the first prospective study to evaluate the pharmacogenetic parameters of low-dose intravenous haloperidol for the treatment of delirium in critically ill adults. We observed a lack of effect on delirium in a population of patients with stable disease severity during the study may be related to lower than expected serum concentration and the presence of important pharmacogenomic confounders. Our results may explain the lack of clinical efficacy of recent randomized trials of low-dose haloperidol. Further studies on genetic subgroups effects on haloperidol serum through levels and effect on individual delirium symptoms (or delirium as a graded syndrome of brain insufficiency rather than delirium being either present or absent) are needed.



Supplemental Digital Content Figure 1: CYP2D6 metrabolizers distribution of haloperidol serum levels across days



Supplemental Digital Content Figure 2: CYP3A4 metrabolizers distribution of haloperidol serum levels across day

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