Pharmacologic Evaluation of Intravenous Haloperidol for the Treatment of Delirium in Critically Ill Adults

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Ethical review	Approved WMO
Status	Pending
Health condition type	Deliria (incl confusion)
Study type	Observational non invasive

Summary

ID

NL-OMON40833

Source
ToetsingOnline

Brief title
Pharmacologics of Haloperidol

Condition

- Deliria (incl confusion)

Synonym
acute confusional state, agitation

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Delirium, Haloperidol, Intensive Care Unit, Pharmacology

Outcome measures

Primary outcome

The primary outcome of this study is to assess whether the maximum ICDSC score achieved each day are related to PK parameters of haloperidol in ICU patients with delirium.

Secondary outcome

- To characterize the association between daily haloperidol serum levels and the resolution of individual delirium symptoms as measured by the daily ICDSC score.

- To characterize the association between daily haloperidol serum levels and the development of each of the following adverse events: a) any increase in the QTc interval from baseline, b) development of akathisia or other extrapyramidal symptoms and c) comedication. This association will be characterized over time.

- To investigate in-patient variability of daily serum levels of scheduled IV haloperidol therapy and explore patient factors that might influence the therapeutic levels achieved. Patients factors that will be evaluated: age, BMI, gender, APACHE-IV score, co-medication and SOFA-score.

- To investigate the influence of CYP3A4 and CYP2D6 genotype on haloperidol serum levels

Study description

Background summary

Delirium is a common form of organ failure in the Intensive Care Unit (ICU). The incidence of delirium at the ICU has been reported to be between 24- 82%, especially in mechanically ventilated and sedated patients. Delirium is associated with higher mortality, longer duration of mechanical ventilation and post-ICU cognitive impairment. In addition, it is estimated that ICU delirium is associated with health care costs ranging from $6 to $20 billion annually in the United States only.

The Intensive Care Delirium Screening Checklist (ICDSC) is a validated screening tool to identify delirium in the critically ill by non-psychiatrists, e.g. trained ICU nurses. Recent evidence suggests that individual delirium symptoms, when evaluated by the ICDSC, resolve differently over time. Furthermore, Devlin et al found that quetiapine (atypical antipsychotic) resolve several delirium symptoms faster than placebo in the Intensive Care Unit. Despite the fact that no randomized, clinical trials exist that support efficacy of antipsychotic drugs for the treatment of delirium in the critically ill and the fact the recent *Clinical Practice for the management of pain, agitation, and delirium in adult patients in the intensive care unit* (SCCM PAD) guidelines do not advocate its use, haloperidol remains the preferred drug among most ICU clinicians for the treatment of delirium. However the pharmacologic response to IV haloperidol when used in critically ill patients with delirium remains poorly characterized. This pertains to both pharmacodynamics (PD) and pharmacokinetics (PK). The pharmacodynamics involve efficacy, (i.e. the resolution of delirium symptoms) and safety (i.e. the incidence of haloperidol-associated adverse effects such as extrapyramidal effects, QTc-interval prolongation etc.). The pharmacokinetics involves exposure to the drug, defined as area under the curve (AUC), maximum concentration in serum (Cmax), half-life (t1/2) and clearance (Cl). Characterization of the pharmacologic response of IV haloperidol will better inform the clinicians on the optimal IV haloperidol dose that should be used to resolve delirium (and the symptoms associated with it) and potentially help reduce the safety concerns associated with its use. Furthermore, such knowledge will help to define optimal dosing schedules for studies on efficacy of IV haloperidol for the resolution of delirium symptoms in critically ill patients. The aim of this study is to characterize the PK and PD of haloperidol in a cohort of critically ill adults managed with a strict medical protocol.

Study objective

The primary outcome of this study is to assess whether the maximum ICDSC score achieved each day is related to PK parameters of haloperidol in ICU patients with delirium.

Secondary outcomes:

- To characterize the association between daily haloperidol serum levels and the resolution of individual delirium symptoms as measured by the daily ICDSC score.
- To characterize the association between daily haloperidol serum levels and the development of each of the following adverse events: a) any increase in the QTc interval from baseline, b) development of akathisia or other extrapyramidal symptoms and c) comedication.This association will be characterized over time.
- To investigate in-patient variability of daily serum levels of scheduled IV haloperidol therapy and explore patient factors that might influence the therapeutic levels achieved. Patients factors that will be evaluated: age, BMI, gender, APACHE-IV score, co-medication and SOFA-score.
- To investigate the influence of CYP3A4 and CYP2D6 genotype on haloperidol serum levels

Study design

Prospective observational cohort study.

Pharmacokinetics of haloperidol
Serum levels of haloperidol will be measured at day 2 at 1, 3, 5, and 7 hours after the first dose of haloperidol. The levels from day 2 will be used to calculate the exposure to haloperidol (by means of an AUC). Trough levels will be measured at day 3, 4, 5, and 6 (end of study) or until haloperidol therapy is stopped before day 6. Trough levels measured at day 3 to 6 will be extrapolated to the AUC measured at day 2. Serum samples (1ml, purple tube) will be drawn from an arterial line and will immediately be sent to the laboratory of the hospital pharmacy and stored at -80 degrees C until analysis. Serum level analysis will be performed by a validated Liquid Chromatography Mass Spectometry Method (LC MS).

Haloperidol metabolism
CYP3A4 and CYP2D6 are the main enzymes involved in the metabolism of haloperidol. Individuals are classified according to the number of active enzyme alleles as: poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM) and ultrarapid metabolizers (UM). CYP2D6 and CYP3A4 genotype will be measured at day 1 of study, the genotype will be used to stratify metabolization rates. A validated method is available in the Laboratory of Clinical Chemistry (AKC). For the analysis a blood sample will be drawn (3 ml, purple tube).

Study burden and risks

Minimal risk is expected for collecting blood samples. Patients will be treated according to standard protocol.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- adult patients (>18 years) with a diagnosis of delirium according to the ICDSC (Intensive Care Delirium Screening Checklist from day 1 of ICU treatment or later (or patients with haloperidol at day of admission, without prior treatment of haloperidol).
- expected ICU-stay of > 48 hours,
- scheduled to be treated with IV haloperidol as per the ErasmusMC ICU delirium treatment protocol

Exclusion criteria

- Treatment with haloperidol in the 24 hours before ICU admission
- ICDSC cannot be obtained due to coma

- end stage liver failure
- primary neurologic disease (if ICDSC score cannot be performed)
- history of severe dementia
- history of parkinsonism and/or psychosis
- a baseline QTc > 450msec at admission
- use of medications with known major interaction with haloperidol (i.e. bosentan, carbamazepine, efavirenz, etravirine, phenobarbital, phenytoin, nevirapine, primidon, rifabutin, lopinavir, ritonavir and rifampicin), patients with delirium caused by acute alcohol withdrawal
- pregnancy

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2014
Enrollment:	40
Type:	Anticipated

Ethics review

Approved WMO

Date:	21-07-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL48875.078.14