Intravenous Haloperidol in the Emergency Department

Opposing authors provide succinct, authoritative discussions of controversial issues in emergency medicine. Authors are provided the opportunity to review and comment on opposing presentations. Each topic is accompanied by an Editor's Note that summarizes important concepts. Participation as an authoritative discussant is by invitation only, but suggestions for topics and potential authors can be submitted to the section editors.

Editor's note: *Haloperidol is frequently administered in the emergency department, but intravenous use has been limited due to "black-box" warnings and concerns about potential toxic side effects. In this Clinical Controversies installment, pro and con advocates present opposing views on the overall safety of intravenous haloperidol, as well as its use in specific patient populations.*

HALOPERIDOL MAY BE SAFELY ADMINISTERED INTRAVENOUSLY IN THE EMERGENCY DEPARTMENT

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Haloperidol is a first-generation antipsychotic medication approved for treating schizophrenia and psychotic disorders; however, it also treats several other challenging conditions commonly encountered in the emergency department (ED).[1] Haloperidol has demonstrated efficacy in acute behavior control, cannabinoid hyperemesis syndrome, and abdominal pain.[2-4] Intravenous (IV) administration allows a rapid onset of action without the delay, pain, and risk of exacerbating agitation associated with intramuscular (IM) administration.[4,5] Though frequently administered IV off-label and approved for IV use in other countries, haloperidol is not approved for IV administration in the United States.[1,6] The Food and Drug Administration (FDA) warned in 2007 about the risk of torsades de pointes and QT prolongation, recommending ECG monitoring if used intravenously.[1,6] Despite this warning, experience and evidence suggest IV administration is safe with appropriate dosing and considering risk factors for QT prolongation.[4,6]

A 2010 review and summary of 70 case reports of QT prolongation and torsades de pointes associated with IV haloperidol demonstrated that 97% of cases had at least 1 concomitant risk factor.[6] Risk factors include age >65 years, cardiac disease, female sex, bradycardia, uncorrected electrolyte abnormalities (eg, hypomagnesemia, hypokalemia, and hypocalcemia), and use of other QT-prolonging medications.[4,6] Reported cumulative doses of haloperidol ranged from 2 mg to 1,540 mg in the literature evaluating these cases of QT prolongation and torsades de pointes.[6] No cases of QT prolongation or torsades de pointes have been reported in those receiving <2 mg IV; 80% occurred in those receiving >10 mg.[6] A 2018 randomized controlled trial using up to 20 mg of IV haloperidol daily for delirium in critical illness showed no increase in the incidence of QT prolongation and no attributable episodes of torsades de pointes compared with placebo.[7] Only those with a corrected QT of ≥550 ms were excluded from receiving IV haloperidol.[7]

In the agitation setting, when nonpharmacologic measures have failed, IV haloperidol has a rapid onset, less pain, better bioavailability than IM administration, and a very low risk of extrapyramidal symptoms.[4-6,8,9] Droperidol is an alternative but is not universally available. Benzodiazepines should be reserved for excited delirium due to sympathomimetics, alcohol withdrawal, or benzodiazepine withdrawal.[9] Though benzodiazepines are not associated with QT prolongation; they are associated with respiratory depression, excessive sedation, and exacerbation of delirium.[5,9,10] The elderly, in particular, are at risk for serious side effects with the use of benzodiazepines, making antipsychotics a better option for agitation and delirium control to facilitate medical evaluation or patient and staff safety.[9,10] The American Geriatrics Society recommends avoiding the use of benzodiazepines for behavior control and reserving antipsychotics like haloperidol for when the patient is a threat to self or others

only when nonpharmacologic measures have failed.[10] Notably, there is a black box warning recommending against the use of any antipsychotics in elderly patients with dementia-related psychosis.[1] While this is a consideration, studies suggesting an increase in mortality in this population were related to longer-term use rather than short-term use in the ED.[1] The American Psychiatric Association practice guideline recommends 1 to 2 mg haloperidol (lower doses of 0.25 to 0.5 mg in elderly) every 2 to 4 hours for delirium requiring pharmacologic treatment with higher IV doses as needed for agitation control.[9] Similarly, IV haloperidol is approved for managing agitation, delirium, and psychosis in many countries, with recommended initial doses ranging from 1 to 10 mg IV.[6]

Haloperidol has been used effectively to treat cannabinoid hyperemesis syndrome and abdominal pain.[2,3] A trial of 33 patients found 0.05 to 0.1 mg/kg haloperidol IV demonstrated superior symptom control compared with ondansetron 8 mg IV. All patients received an ECG prior to enrollment, and there were no cases of QT prolongation or torsades de pointes.[2] A trial including 107 patients with self-matched encounters found haloperidol was associated with reduced administration of morphine equivalents and lower rates of rescue therapy in patients with abdominal pain.[3] Over 87% of patients received haloperidol via the IV route.[3] A 2017 randomized, double-blind, placebo-controlled trial included patients with gastroparesis receiving haloperidol versus conventional therapy. Authors found IV haloperidol reduced pain and nausea at one hour.[11]

Based on the available evidence, IV haloperidol may be safely administered for acute agitation, psychotic disorders, cyclical vomiting, abdominal pain, and gastroparesis in the ED. The FDA warning should be updated to reflect the most recent evidence demonstrating a cumulative dose of $\leq$2 mg IV haloperidol does not require an ECG or additional monitoring.[4,6] Overall, significant QT prolongation and torsades de pointes associated with IV haloperidol use are rare events, but several precautions are recommended.[4,6] In those with multiple risk factors for torsades de pointes or currently receiving QT-prolonging medications, a baseline ECG to assess the corrected QT is recommended; a post treatment ECG is recommended at peak dose (30 to 60 minutes) if a higher dose (eg, >5 mg) of IV haloperidol is administered.[4,6] In practice, an ECG may often occur after medication administration in agitated patients. Telemetry monitoring is only recommended for those at high risk for torsades de pointes, such as patients with a corrected QT of >500 ms on baseline or post treatment ECG or in those receiving repeated high doses of haloperidol (eg, >100 mg).[4] Haloperidol should be discontinued if the corrected QT is >550 ms.[7]

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INTRAVENOUS HALOPERIDOL HAS A LIMITED ROLE IN THE MODERN EMERGENCY DEPARTMENT

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