Intramuscular Midazolam, Olanzapine, Ziprasidone, or Haloperidol for Treating Acute Agitation in the Emergency Department

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Study objective: Agitation in the emergency department (ED) can pose a threat to patient and provider safety; therefore, treatment is indicated. The purpose of this study is to compare haloperidol, olanzapine, midazolam, and ziprasidone to treat agitation.

Methods: This was a prospective observational study of consecutive patients receiving intramuscular medication to treat agitation in the ED. Medications were administered according to an a priori protocol in which the initial medication given was predetermined in the following 3-week blocks: haloperidol 5 mg, ziprasidone 20 mg, olanzapine 10 mg, midazolam 5 mg, and haloperidol 10 mg. The primary outcome was the proportion of patients adequately sedated at 15 minutes, assessed with the Altered Mental Status Scale.

Results: Seven hundred thirty-seven patients were enrolled (median age 40 years; 72% men). At 15 minutes, midazolam resulted in a greater proportion of patients adequately sedated (Altered Mental Status Scale <1) compared with ziprasidone (difference 18%; 95% confidence interval [CI] 6% to 29%), haloperidol 5 mg (difference 30%; 95% CI 19% to 41%), haloperidol 10 mg (difference 28%; 95% CI 17% to 39%), and olanzapine (difference 9%; 95% CI −1% to 20%). Olanzapine resulted in a greater proportion of patients adequately sedated at 15 minutes compared with haloperidol 5 mg (difference 20%; 95% CI 10% to 31%), haloperidol 10 mg (difference 18%; 95% CI 7% to 29%), and ziprasidone (difference 8%; 95% CI −3% to 19%). Adverse events were uncommon: cardiac arrest (0), extrapyramidal adverse effects (2; 0.3%), hypotension (5; 0.5%), hypoxemia (10; 1%), and intubation (4; 0.5%), and occurred at similar rates in each group.

Conclusion: Intramuscular midazolam achieved more effective sedation in agitated ED patients at 15 minutes than haloperidol, ziprasidone, and perhaps olanzapine. Olanzapine provided more effective sedation than haloperidol. No differences in adverse events were identified. [Ann Emerg Med. 2018;■:1-12.]

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INTRODUCTION

Background

Agitation is commonly encountered in the emergency department (ED) and can range from psychomotor restlessness to overt aggression and violent behavior.[1] In the ED, the cause of agitation is often undifferentiated and can be a consequence of alcohol intoxication, drug intoxication, psychiatric illness, or underlying medical illness. Early efforts in the ED should include identifying and treating any reversible causes, but in many cases of behavioral disturbance, intervention is indicated to reduce the risk of serious harm to patients and to ED staff. Initial interventions to treat agitation may include noncoercive approaches such as verbal de-escalation,[2,3] but these techniques may not be successful and parenteral medications may be necessary.[4-7]

Importance

There is no consensus on the ideal parenteral sedative agent for acute agitation in the ED in regard to efficacy and safety profiles.[4] Commonly used medications include antipsychotics (eg, haloperidol, ziprasidone, olanzapine) and benzodiazepines (eg, midazolam, lorazepam, diazepam).[4-7] Droperidol had previously been a popular

Editor's Capsule Summary

What is already known on this topic

Emergency physicians often treat acutely agitated patients with antipsychotics or benzodiazepines.

What question this study addressed

Is adequate sedation more frequent with intramuscular haloperidol 5 mg, haloperidol 10 mg, ziprasidone 20 mg, olanzapine 10 mg, or midazolam 5 mg?

What this study adds to our knowledge

In this comparative trial of 737 adults with acute agitation, more patients who received midazolam (71%) compared with any of the antipsychotics (range 40% to 61%) were adequately sedated at 15 minutes.

How this is relevant to clinical practice

Intramuscular midazolam 5 mg appears superior to standard doses of antipsychotics when used for sedating acute agitated adults.

choice but has been largely unavailable in the United States since 2013 because of a national drug shortage.[8-10]

The existing evidence comparing medications to treat agitation is limited by several factors, which include a relative paucity of studies set in the ED compared with the psychiatric inpatient setting, as well as the use of intravenous delivery of study sedatives, which is not always feasible for acutely agitated patients.[11-13] Other limitations arise from the external validity of studies performed outside the United States that use droperidol as a study arm because it is no longer domestically available,[11-16] or the use of drugs through routes that are not currently approved by the Food and Drug Administration (FDA), such as intravenous olanzapine.[11,12,17] A trial comparing intramuscular sedatives commonly used in the ED would help inform the care of acutely agitated patients.

Goals of This Investigation

The purpose of this investigation was to compare intramuscular olanzapine, haloperidol, ziprasidone, and midazolam for treating acute agitation in a prospective observational cohort of consecutive ED patients. These 4 intramuscular medications have not previously been studied in a comparative manner, to our knowledge. Specifically, we sought to identify which medication achieved the most effective sedation after 15 minutes because rapid sedation is essential for patient and provider safety.

MATERIALS AND METHODS

Study Design and Setting

This study was conducted from June 2017 to October 2017 at Hennepin County Medical Center in Minneapolis, MN. The study hospital is an inner-city Level I adult and pediatric trauma center, with greater than 100,000 annual visits. The hospital experiences large volumes of visits for alcohol and illicit substance intoxication (>7,000 per year).[18] There is a geographically distinct acute psychiatric emergency services department, which has visits mostly for isolated psychiatric complaints, and will generally not treat patients with concomitant intoxication or agitation.

This study was initially presented to our institutional review board as a prospective, double-blind, randomized, clinical trial. Clinical investigations of drugs in which the patient is unable to provide informed consent (as is the case in acute agitation)[19] require protections afforded by exception from informed consent (21 CFR 50.24) regulations.[20-22] In addition to local institutional review board approval, implementation of an exception from informed consent study requires community consultation sessions, public disclosure, and approval from the FDA in the form of an Investigational New Drug application.[23] We completed 3 community consultation sessions without any significant concerns raised, and our institutional review board provisionally approved the randomized clinical trial (pending FDA acceptance). However, the FDA ultimately did not approve the Investigational New Drug application, citing that there was insufficient evidence that this population could not provide informed consent, so we were therefore unable to proceed with the randomized trial design as intended.

Because all 4 medications of interest proposed in this trial were considered standards of care, and the relative risks between treatments were minimal, our ED instead implemented a clinical care protocol guiding agitation treatments. With this protocol, for a 15-week period, all adult patients (≥18 years) who required treatment for acute agitation received initial treatment with a prespecified medication, determined a priori. The prespecified medication changed every 3 weeks. The treating physician was responsible for determining whether the patient needed to be treated for agitation, but the clinical protocol dictated which initial medication would be given. All treatment choices after the initial medication were at the discretion of the physician. An observational study describing the implementation of this clinical care