Midazolam-Droperidol, Droperidol, or Olanzapine for Acute Agitation: A Randomized Clinical Trial

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Study objective: We aim to determine the most efficacious of 3 common medication regimens for the sedation of acutely agitated emergency department (ED) patients.

Methods: We undertook a randomized, controlled, double-blind, triple-dummy, clinical trial in 2 metropolitan EDs between October 2014 and August 2015. Patients aged 18 to 65 years and requiring intravenous medication sedation for acute agitation were enrolled and randomized to an intravenous bolus of midazolam 5 mg - droperidol 5 mg, droperidol 10 mg, or olanzapine 10 mg. Two additional doses were administered, if required: midazolam 5 mg, droperidol 5 mg, or olanzapine 5 mg. The primary outcome was the proportion of patients adequately sedated at 10 minutes.

Results: Three hundred forty-nine patients were randomized to the 3 groups. Baseline characteristics were similar across the groups. Ten minutes after the first dose, significantly more patients in the midazolam-droperidol group were adequately sedated compared with the droperidol and olanzapine groups: differences in proportions 25.0% (95% confidence interval [CI] 12.0% to 38.1%) and 25.4% (95% CI 12.7% to 38.3%), respectively. For times to sedation, the differences in medians between the midazolam-droperidol group and the droperidol and olanzapine groups were 6 (95% CI 3 to 8) and 6 (95% CI 3 to 7) minutes, respectively. Patients in the midazolam-droperidol group required fewer additional doses or alternative drugs to achieve adequate sedation. The 3 groups’ adverse event rates and lengths of stay did not differ.

Conclusion: Midazolam-droperidol combination therapy is superior, in the doses studied, to either droperidol or olanzapine monotherapy for intravenous sedation of the acutely agitated ED patient. [Ann Emerg Med. 2016;:1-9.]

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INTRODUCTION

Background

Acute agitation among emergency department (ED) patients is often associated with recreational drug or alcohol intoxication, mental illness, or combinations of diagnoses.1-5 The agitation may escalate to violence that is disruptive and associated with a risk of injury to the patient and individuals around them.5,6 These events usually result in a “security code” being called for an unarmed threat. De-escalation techniques are recommended initially,7 although parenteral medication sedation may be required.1,3,5,6

Importance

Sedation for acute agitation is required in 3 to 20 cases for every 1,000 ED presentations3,6 and the risk to the patient is real. Adverse effects are common and include airway compromise, oxygen desaturation, hypotension, and extrapyramidal events.3,5,8-12 The challenge is to use a medication regimen that will rapidly and effectively sedate the patient without putting him or her at substantial risk of adverse events. To date, a wide range of regimens has been used, mostly including benzodiazepines or antipsychotic medications administered by either the intramuscular or intravenous route.4,8,9,13-15

Most studies of acute agitation have been undertaken in the psychiatric setting. Hence, most evidence is not directly applicable to the ED, where the onset of sedation needs to be rapid and where the pathogenesis of the agitation is often undifferentiated.3 Currently, ED sedation guidelines are often inconsistent, poorly supported by evidence, and frequently not followed.13 Furthermore, sedation practice is evolving, with new medications being incorporated into practice in unapproved settings or routes of administration, eg, intravenous olanzapine.16
Editor’s Capsule Summary

What is already known on this topic
Emergency physicians often treat acutely agitated patients with antipsychotics, benzodiazepines, or both.

What question this study addressed
Is adequate sedation after 10 minutes more frequent with droperidol 10 mg, olanzapine 10 mg, or midazolam 5 mg plus droperidol 5 mg?

What this study adds to our knowledge
In this randomized controlled trial of 349 adults with acute agitation, at 10 minutes after administration, 25% more patients in the midazolam-droperidol group had achieved adequate sedation than had the group with the other agents, with a similar frequency of adverse events.

How this is relevant to clinical practice
Combination midazolam 5 mg plus droperidol 5 mg is more effective for acute agitation than either droperidol 10 mg or olanzapine 10 mg.

Goals of This Investigation
Recent research suggests that medication combination regimens are superior to monotherapy.1,13,15 Chan et al1 reported that both intravenous midazolam-droperidol and intravenous midazolam-olanzapine combinations are superior to intravenous midazolam monotherapy. The relevance of this finding is that benzodiazepine monotherapy, especially midazolam, is currently the most commonly used regimen for acute agitation management in some parts of the world.1,13,15 Droperidol4,13,15 and, more recently, olanzapine4,12,16,17 are also used as monotherapy. To date, the efficacy of the midazolam-droperidol combination in acute agitation has not been compared with either droperidol or olanzapine monotherapy. We compared these 3 regimens and hypothesized that the midazolam-droperidol combination would be the superior regimen.

MATERIALS AND METHODS
Study Design and Setting
We undertook a randomized, controlled, double-blind, triple-dummy, clinical trial in the EDs of 2 inner-city, tertiary-referral, Australian hospitals with an annual census of 45,000 adult patients for one and 70,000 for the other. Each ED is supported by 24 hour colocated psychiatric services. Patients were enrolled between October 2014 and August 2015. The trial was registered on the Australian and New Zealand Clinical Trials Registry and approved by the human research ethics committees of the participating institutions.

Selection of Participants
Patients were eligible for inclusion if they were aged 18 to 65 years and required intravenous medication sedation for acute agitation, as determined by their attending emergency physician. Patients were excluded if they had been previously enrolled, had a known hypersensitivity or contraindication to a study medication, had a reversible cause for their agitation (hypotension, hypoxia, or hypoglycemia), were experiencing acute alcohol withdrawal, or were pregnant.

Enrollment was based on patient and staff safety considerations and not sedation scores. Patients who received a sedative medication within the previous 12 hours, either as usual medications or out-of-hospital treatment, were eligible if they met other eligibility criteria. Because of the level of agitation, informed patient consent was not possible and human research ethics committee approval was given for waiver of consent.

Methods of Measurement
Patients were assigned to a midazolam-droperidol combination arm, a droperidol monotherapy (droperidol) arm, or an olanzapine monotherapy (olanzapine) arm (Figure 1). The first and additional doses, respectively, were midazolam 5 mg plus droperidol 5 mg and midazolam 5 mg, droperidol 10 and 5 mg, and olanzapine 10 and 5 mg (Appendix E1, available online at http://www.annemergmed.com). Doses were determined from clinical practice13,16,17 and previous trials1,5 and were administered by rapid intravenous push. The midazolam-droperidol combination was chosen over midazolam-olanzapine because droperidol is more commonly used.13,18

Study packs were assembled by the pharmacy department of a third hospital. Each contained a patient identification code, instructions, a case report form, vials of repackaged medication or placebo, water for reconstitution, normal saline solution for dilution, disposables (eg, needles, syringes), and a sealed envelope with a description of the vial contents (if unblinding were required).

At each site, study packs were block randomized in groups of 6 (2 for each study arm) to ensure approximately equal numbers of patients in each arm. A pharmacist not involved with patient enrollment, data collection, or data analysis conducted the randomization with random-number tables and kept the codes confidential.

Midazolam and droperidol are clear liquids. Olanzapine is a yellow powder that requires reconstitution to a yellow liquid. To achieve blinding, a triple-dummy technique was
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