Randomized Clinical Trial Comparing Intravenous Midazolam and Droperidol for Sedation of the Acutely Agitated Patient in the Emergency Department

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Study objective: We compare intravenous midazolam and droperidol for the onset of sedation of acutely agitated patients in the emergency department (ED).

Methods: This was a double-blind, randomized, clinical trial set in the ED of a university teaching hospital. Subjects were adults, acutely agitated because of mental illness, intoxication, or both, who received midazolam or droperidol, 5 mg intravenously, every 5 minutes until sedated. We analyzed time to sedation using survival analysis, median times to sedation, and proportions sedated at 5 and 10 minutes.

Results: Seventy-four patients received midazolam; 79 patients, droperidol. Survival analysis showed no difference in time to sedation (hazard ratio 0.86; 95% confidence interval [CI] 0.61 to 1.23), \( P = .42 \). Median time to sedation was 6.5 minutes for midazolam (median dose 5 mg) and 8 minutes for droperidol (median dose 10 mg), \( P = .075 \) (effect size 1.5 minutes; 95% CI 0 to 4 minutes). At 5 minutes, 33 of 74 (44.6%) patients from the midazolam group were adequately sedated compared with 13 of 79 (16.5%) patients from the droperidol group, a difference of 28.1% (95% CI 12.9% to 43.4%; \( P < .001 \)). By 10 minutes, 41 of 74 (55.4%) from the midazolam group were sedated compared to 42 of 79 (53.2%) from droperidol, a difference of 2.2% (95% CI –14.9% to 19.3%; \( P = .91 \)). Eleven adverse events occurred in the midazolam group and 10 in the droperidol group. Three patients required active airway management (3 patients with assisted ventilation and 1 patient intubated); all received midazolam.

Conclusion: There is no difference in onset of adequate sedation of agitated patients using midazolam or droperidol. Patients sedated with midazolam may have an increased need for active airway management. [Ann Emerg Med. 2006;47:61-67.]

INTRODUCTION

Background

The management of acutely agitated patients, whether because of psychiatric illness or drug or alcohol intoxication, results in a disproportionate use of emergency department (ED) resources. A number of techniques are used to placate such patients, including setting limits, clear explanations of procedures, and chemical and physical restraint. Restraints are used only when individuals are at risk of harming themselves or those around them, including staff and other patients, and is required in 0.3% to 2% of all ED presentations.1,2 Reviews of Australasian, United Kingdom, and US restraint practices indicate that the drugs used for restraint in the ED are neuroleptics and short-acting benzodiazepines.1,3,4

The majority of acute sedation studies has examined the management of acute agitation in psychiatric wards or ICUs. These settings often require long sedation times, often measured in hours, and either lack applicability to the general ED population or lack the power to exclude differences between agents.5,8 Benzodiazepines are effective sedatives, with midazolam and diazepam (but not lorazepam) available parenterally in Australia, and are used frequently as first-line agents.1 Alternatives include the neuroleptics; droperidol has been shown to be more effective as a sedative compared with haloperidol.7,9 For rapid tranquillization requiring intravenous administration, midazolam and droperidol have gained ascendancy in Australasian EDs.1,2
Goals of This Investigation

Midazolam and droperidol have not been compared for treatment of acutely agitated patients. The aim of this study is to compare these agents with respect to time to adequate sedation, the need for subsequent sedation within 60 minutes, and adverse event rates. We hypothesized that there would be no difference between the drugs with respect to these outcomes.

MATERIALS AND METHODS

Study Design and Setting

The study was a double-blind, randomized, clinical trial of intravenous midazolam versus droperidol conducted in the ED of a large Australian metropolitan university hospital with approximately 50,000 attendances annually.

Selection of Participants

Patients were eligible for enrollment if they were aged 18 to 65 years (inclusive) and exhibited marked agitation that required chemical restraint as deemed by a consultant (attending) emergency physician or a senior accredited resident of the Australasian College for Emergency Medicine. If the age of the patient was unknown at enrollment, the patient was eligible if judged to be aged 18 to 65 years by the treating physician.

Exclusion criteria were known hypersensitivity to either drug, known pregnancy, or readily reversible causes for the agitation (systolic blood pressure < 90 mm Hg, hypoxia, hypoglycemia). If the treating physician believed the agitation was due to acute alcohol withdrawal, the patient was also excluded because this condition is particularly amenable to treatment with benzodiazepines.

Consent was not required from the patients for enrollment, because these drugs and dosages are standard for management of acute agitation in our ED, and the decision to sedate the patient was taken if he or she no longer had decision-making capacity.

This study was approved by the Royal Melbourne Hospital Clinical Research and Ethics Committee. Informed consent was specifically not required from the patients, and no limitations were placed by the ethics committee.

Interventions

The hospital pharmacy prepared 20 mg of either drug in 4-mL clear solutions. These solutions were packaged in identical vials and randomly assigned to serially numbered study packs. Randomization was determined from random-number tables, and the codes remained with pharmacy until the study was complete. The packs also contained the study documentation and were distributed sequentially to consecutively enrolled patients.

Enrolled patients had an intravenous cannula inserted and were moved to a monitored area of the ED. The sedative solution was prepared with the addition of 16 mL of normal saline solution to give 20 mg in a 1 mg/mL concentration. Patients were given 5-mg doses by intravenous push every 5 minutes until adequate sedation was achieved. For patients less than 50 kg, the dose was 2.5 mg.

Any medication (including sedatives), procedure, or other therapy thought to be necessary for the safe treatment of the patient could be administered as judged by the attending physician.

If the full dose of 20 mg of sedative was given without adequate sedation, the physician was free to choose subsequent therapy for sedation.

If necessary for patient treatment, unblinding of the drug could be achieved by opening a sealed envelope contained in the study pack. Return of the sealed envelope to the study investigators was mandatory to ensure blinding was maintained.

A blinded explicit review of the patient’s medical record was performed after discharge from the ED.

Outcome Measures

The primary endpoint assessed was time to sedation, defined as the time from the initial dose of drug until a score of 2 or less on a 6-point agitation scale (5, highly aroused and violent; 4, highly aroused; 3, moderately aroused; 2, mildly aroused and pacing; 1, settled; 0, asleep) was achieved. The scale was developed to monitor changes in agitation levels and is similar to the scale used in previous agitation research.

Comparison...
was made between the time to sedation using each drug and the proportion of patients sedated at 5 and 10 minutes.

The dose and time of drug administration, patient’s vital signs, ECG, and adverse events were recorded contemporaneously by the nurse treating the patient. Agitated patients requiring restraint have 1:1 nursing, which allows continual observation and the onset of sedation to be recorded to the nearest minute.

Observations of pulse rate, blood pressure, and oxygen saturation were recorded at 0, 5, 10, 15, and 30 minutes and then every 15 minutes until 60 minutes after adequate sedation was achieved. A 12-lead ECG was obtained within 30 minutes of adequate sedation being achieved. Because of the difficulty of obtaining an ECG on an uncooperative patient, a preintervention ECG was not required.

Secondary endpoints were the need for subsequent sedation within 60 minutes of initial (adequate) sedation, the corrected QT (QTc) interval on a 12-lead ECG, and adverse event rates. These data were obtained from the patient’s medical record. Adverse events were recorded in the study documentation by the nurse attending the patient. The patient’s medical record was also subsequently reviewed to identify adverse events. Adverse events were defined and specified on the study documentation. They were active airway management (eg, jaw thrust, oral or nasal airway), assistance with ventilation (eg, bag and mask), oxygen required for documented desaturation below 90%, systolic blood pressure less than 90 mm Hg, documented arrhythmia, dystonic reaction, seizure, vomiting, or aspiration of stomach contents.

Data Collection and Processing

The ED nurse responsible for the patient recorded the time of the first and subsequent doses, the time that adequate sedation was achieved, and any adverse events on the study documentation.

One investigator (JK), still blinded, subsequently extracted from the patients’ records their vital signs, QTc interval, need for subsequent sedation, and any adverse events as defined in the protocol. The patient’s final diagnosis was obtained, as well as details of any drug or alcohol intoxication, identified clinically or by laboratory testing (alcohol >0.05% [g/100 mL]). A diagnosis of mental illness was defined by International Classification of Diseases, 10th Revision codes F09 to F69 and F99, excluding those codes for simple intoxications. Coding was performed by the Health Information Department of the hospital.

Primary Data Analysis

The sample size calculation was based on detecting a clinically important mean difference of 5 minutes to sedation (SD of 15 minutes, a error of 0.05, and a b error of 0.2). Accordingly, 140 patients were required in each arm. A planned interim analysis was conducted at the midpoint of the trial, and because of the results from the 153 patients enrolled at that stage, the study was concluded.

Analysis was conducted on an “intention-to-treat” analysis using Stata, version 8.2 (Stata Corporation, College Station, TX). Time to sedation was analyzed as survival-time data using the Cox’s proportional hazards model, the median times to sedation were compared using the Wilcoxon rank-sum test, and the proportion of patients sedated at 5 and 10 minutes was compared using \( \chi^2 \) tests. For the secondary endpoints, the need for alternate medications to achieve sedation, the need for subsequent medication within 60 minutes of sedation, and the adverse event rates were assessed using \( \chi^2 \) or Fisher’s exact test as appropriate. QTc intervals were analyzed with the Wilcoxon rank-sum test, and confidence intervals (CIs) for the difference in medians were calculated using the Stata command `cendif`.

RESULTS

Characteristics of Study Subjects

One hundred seventy patients were enrolled by study-pack allocation. Of these, 17 packs were lost so that data on 153 patients were available for analysis (Figure 1). Table 1 shows patient characteristics; there were no significant differences between the patients in each arm of the trial. A number of patients sedated before their full details became available were subsequently found to be outside the age inclusion criteria (18 to 65 years). Six patients in the midazolam arm were aged 15, 17, 17, 66, 67, and 67 years. Five droperidol patients were aged 16, 16, 16, 17, and 76 years. These patients were included in the analysis.
Main Results

Seventy-four patients received midazolam, and 79 patients received droperidol. Survival analysis showed no difference in time to sedation (Figure 2). The median time to sedation for midazolam was 6.5 minutes (median dose 5 mg) compared with 8 minutes for droperidol (median dose 10 mg), \( P = 0.075 \) (effect size 1.5 minutes; 95% CI 0 to 4 minutes). The proportion of patients sedated by 5 minutes after midazolam treatment was 44.6% (95% CI 33.0% to 56.3%) compared with 65.7% (95% CI 56.0% to 75.5%) for droperidol. The difference between the 2 groups was 20.1% (95% CI 10.4% to 30.9%; \( P < 0.001 \)).

Despite initial adequate sedation, further agitation requiring recurrent sedation was required within 60 minutes for 10.1% (8 of 79) of patients who received droperidol. However, by 60 minutes, 41 of 74 (55.4%) of the midazolam group were sedated compared with 42 of 79 (53.2%) of the droperidol group, a difference of 2.2% (95% CI −14.9% to 19.3%; \( P = 0.91 \)).

Adverse events reported up to 60 minutes after sedation are shown in Table 2. The midazolam group had 11 adverse events, including the need for active airway management in 3 patients (4.1%). All 3 patients required assisted ventilation with a bag and mask circuit; 1 of these patients required intubation for apnea. There were 10 adverse events in the droperidol group, including 3 dystonic reactions (3.8%) and 1 arrhythmia (1.3%). The arrhythmia was a bradycardia with a rate of 50 beats/min (from a baseline of 60 to 50 beats/min). The patient’s blood pressure remained in normal limits, and management was by observation only.

Cardiovascular characteristics were assessed at 30 and 60 minutes after sedation and are reported in Figure 3. Although overall there were no significant differences in the cardiovascular effects of the 2 drugs, patients receiving midazolam tended to have a higher pulse rate and larger decreases in systolic blood pressure postsedation (including 1 patient with a systolic drop of 95 mm Hg from 170 mm Hg).

An ECG was obtained within 30 minutes of sedation in 108 patients. The median QTc was 425 ms (range 382 to 507 ms) for the 56 patients who received midazolam and 439 ms (range 352 to 516 ms) for 52 patients who received droperidol (Figure 4). The difference in medians is 14 ms (95% CI 5 to 22 ms).

Table 1. Patient characteristics and indications for restraint.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Midazolam (N=74)</th>
<th>Droperidol (N=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>35 (15–67)</td>
<td>32 (16–76)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>47 (64)</td>
<td>51 (65)</td>
</tr>
<tr>
<td>Intoxication, No. (%)</td>
<td>28 (38)</td>
<td>33 (42)</td>
</tr>
<tr>
<td>Alcohol, No. (%)</td>
<td>26 (35)</td>
<td>26 (33)</td>
</tr>
<tr>
<td>Drugs, No. (%)</td>
<td>7 (9)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Mental illness, No. (%)</td>
<td>47 (64)</td>
<td>53 (67)</td>
</tr>
<tr>
<td>Initial dose (mg)</td>
<td>5 (2.5–20)</td>
<td>5 (2–10)</td>
</tr>
<tr>
<td>Total dose (mg)</td>
<td>5 (2.5–20)</td>
<td>10 (2–20)</td>
</tr>
</tbody>
</table>

Table 2. Adverse event rates postsedation.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Midazolam (N=74)</th>
<th>Droperidol (N=79)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway management</td>
<td>3 (4.1)</td>
<td>0</td>
<td>−4.1 (−9.9 to 1.8)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>4 (5.4)</td>
<td>3 (3.8)</td>
<td>−1.6 (−9.6 to 6.4)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4 (5.4)</td>
<td>3 (3.8)</td>
<td>−1.6 (−9.6 to 6.4)</td>
</tr>
<tr>
<td>Arrhythmia (bradicardia)</td>
<td>0</td>
<td>1 (1.3)</td>
<td>1.3 (−2.5 to 5.0)</td>
</tr>
<tr>
<td>Dystonic reaction</td>
<td>0</td>
<td>3 (3.8)</td>
<td>3.8 (−1.7 to 9.3)</td>
</tr>
<tr>
<td>Assistance with</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ventilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aspiration</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Seizure</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>11 (14.9)</td>
<td>10 (12.7)</td>
<td>−2.2 (−14.5 to 10.0)</td>
</tr>
</tbody>
</table>

Table 2. Adverse event rates postsedation.
500 ms, 2 in the midazolam group and 1 in the droperidol group; none had an adverse event.

Four study packs were unblinded, 2 in each arm, because the treating physician needed to determine which drug had been given. In 3 cases, this was in response to significant adverse events related to airway management; adequate sedation had been achieved. The patients were treated with airway and ventilatory support; flumazenil was not given. One droperidol pack was unblinded after all 20 mg had been given, without adequate sedation, to inform further sedation.

LIMITATIONS

A number of limitations in this study have been identified. Selection bias may have occurred if physicians failed to enroll patients for whom they had a particular preference in terms of pharmacologic management. It was difficult to determine the number of eligible patients not enrolled. In our department, it is likely to be low because midazolam and droperidol are the preferred sedation agents and used interchangeably on an ad hoc basis; it is uncommon for a particular preference for either drug to occur.

The time to sedation was somewhat subjective and determined by a large number of nurses. However, patients and staff remained blinded to which drug was used throughout each patient’s stay.

**Figure 3.** Cardiovascular characteristics at 30 and 60 minutes after sedation. Box denotes 25**th** to 75**th** percentile, whiskers 1.5 × IQR. Change is equal to 30 (or 60) minute reading minus 0-minute reading.

**Figure 4.** QTc on ECG within 30 minutes of adequate sedation. Box denotes 25**th** to 75**th** percentile, whiskers 1.5 × IQR.
Seventeen study packs were lost. It is not known whether these were selected and discarded unused or used for sedation, with all documentation subsequently lost.

Four study packs were unblinded to allow the treating physician to manage adverse events or inform further sedation. Although it would have been possible to prevent unblinding of the drugs in this study, the treatment of this patient population is complex, and the potential for adverse events is high. We believed that the research protocol should yield to clinical practice, including knowledge of drugs administered, where necessary.

Although patients were to have an ECG within 30 minutes of sedation, not all patients did, and there was some variation around when this test was conducted. There were also differences between the time of the first drug dose and the time of the ECG because of variation in time to achieving adequate sedation. As a result, the QTc measured may not have been the maximum QTc for each patient.

The study was inadequately powered to compare differences in specific adverse events such as dystonic reactions or the need for airway management. Although there was minimal difference between the 2 groups in total adverse event rates, a larger study is required for detailed examination of differences.

DISCUSSION

We believe this to be the first blinded, randomized, clinical study comparing midazolam and droperidol for rapid sedation of agitated patients in a general ED. There was no difference in the time to sedation; however, more patients were sedated in the first 5 minutes when midazolam was used.

The TREC collaborative group (Rio) and Nobay et al found midazolam results in a shorter time to sedation than a neuroleptic. However, those studies used intramuscular haloperidol, and haloperidol has been shown to have slower onset of sedation for the acutely agitated patient compared to droperidol. Intramuscular administration will also slow time to adequate sedation and is less amenable to titration than intravenous dosing, which is reflected in the time for sedation within these studies of 20 to 60 minutes.

The only other study to evaluate rapid sedation in a general ED was conducted by Richards et al using intravenous droperidol and lorazepam. That study was open label and found no difference in sedation scores at 5 minutes. Nobay et al showed that intramuscular midazolam (18.3±14 minutes) was more effective than intramuscular lorazepam (32.2±20 minutes) in achieving sedation.

Droperidol has a long history as an agent for sedation and antiemesis. It received a “black box” warning from the US Food and Drug Administration (FDA) in 2001 because of concerns about prolongation of the QTc. Our study showed that patients who received droperidol had a longer QTc than those receiving midazolam. However, the effect is unlikely to be clinically significant, with only 1 patient receiving droperidol having a QTc greater than 500 ms compared with 2 patients who had received midazolam. Of note, the only patient to have a documented arrhythmia, prolonged bradycardia, had received droperidol, although the QTc was within the normal range. It was impossible to obtain a QTc on this highly agitated population before sedation. Subsequent to the FDA warning, there have been several reports indicating that droperidol is a safe drug. There is unlikely to be an ideal drug developed that can provide rapid tranquillization of the undifferentiated, severely agitated patient without potential for adverse effects.

In this study, midazolam achieved adequate sedation in more patients in the first 5 minutes, and there was no significant difference between adverse event rates. However, it is worth noting the different adverse event profile. Although similar rates of hypoxia were observed for both drugs, 3 patients in the midazolam arm required active airway management, which is consistent with our current practice of restricting the use of intravenous benzodiazepines to critical care areas that can provide airway support. As expected, droperidol was associated with dystonic reactions in a small proportion of patients.

Patients who received midazolam were more likely to require further sedation within 60 minutes than those receiving droperidol, which may or may not be advantageous, depending on the clinical situation, specifically whether prolonged sedation or rapid recovery is preferred.

In summary, intravenous midazolam and droperidol are equally effective sedating agents, with more than half the patient population able to be sedated within 10 minutes. Midazolam achieved adequate sedation in more patients in the first 5 minutes, although its use may be associated with an increased requirement for active airway support and an increased need for further sedation within 60 minutes.

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Author contributions: JK was principal investigator. JK, DT, and DC were responsible for initial study design. JK conducted the study and collected the data. JK, DT, and DC conducted data analysis and manuscript preparation. JK was principally responsible for the statistical analysis of the data. JK takes responsibility for the paper as a whole.

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