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Parenteral sedation of elderly patients with acute behavioral disturbance in the emergency department

Running Title: Sedation of elderly patient with acute behavioral disturbance

Leonie Calver[1], Geoffrey K. Isbister[1] MD

[1] Discipline of Clinical Pharmacology, University of Newcastle and Department of Clinical Toxicology and Pharmacology, Calvary Mater Newcastle, New South Wales, Australia;

Corresponding Author: Geoff Isbister, c/o Calvary Mater Newcastle, Edith St, Waratah NSW, Australia 2298; Tel: +612 4921 1211; Fax: +612 4921 1870;

Email: geoff.isbister@gmail.com

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Abstract

Purposes: This study aimed to investigate sedation of elderly patients with acute behavioral disturbance (ABD) in the emergency department, specifically the safety and effectiveness of droperidol.

Basic Procedures: This was a prospective study of elderly patients (>65y) with ABD requiring parenteral sedation and physical restraint in the emergency department. Patients were treated with a standardized sedation protocol that included droperidol. Drug administration, time to sedation, additional sedation and adverse effects were recorded. Effective sedation was defined as a drop in the sedation assessment tool score by two or a score of zero or less.

Main findings: There were 49 patients: median age 81y (Range:65-93y); 33 were males. Thirty patients were given 10mg droperidol, 15 were given 5mg droperidol, two were given 2.5mg and two were given midazolam. Median time to sedation for patients receiving 10mg droperidol was 30min (IQR:18-40 min), compared to 21min (IQR:10-55min;p=0.55) for patients receiving 5mg droperidol. Three patients were not sedated within 120min. Eighteen patients required additional sedation – 10/30 (33%;95%CI:18-53%) given droperidol 10mg compared to 7/15 (47%;95%CI:22-73%) given 5mg. Fourteen patients required re-sedation. Adverse effects occurred in 5 patients (hypotension[2], over-sedation[2], hypotension/over-sedation[1]) - 2/30 given 10mg droperidol and 3/19 not treated according to protocol. Midazolam was given initially or for additional sedation in two of five adverse effects. No patient had QT prolongation.

Principal Conclusions: Droperidol was effective for sedation in most elderly patients with ABD and adverse effects were uncommon. An initial 5mg dose appears prudent with the expectation that many will require another dose.

Introduction

Acute behavioral disturbance (ABD) in the elderly is a difficult management problem in the emergency department. In addition to the difficulties with treating any patient with ABD, there is a higher incidence of co-morbidity in elderly patients, including them being on multiple medications.[1] Most elderly patients with ABD settle with various strategies used to calm, orientate and settle disturbed behavior. However, a small number remain at risk to themselves and/or others and require parenteral sedation and physical restraint to ensure the safety of the patient and staff.[2]

It remains unclear what the best agents are for parenteral sedation of ABD in the elderly,[3] and if a dose reduction is required.[4] There are no studies of ABD in elderly emergency department patients,[5] and there is no specific drug therapy approved by the United States Food and Drug Administration (FDA).[2] Although the literature supports the current preference for antipsychotics over benzodiazepines,[6-8] there are no trials supporting this. Establishing an effective and safe medication for parenteral sedation of the elderly is essential to providing rapid diagnosis and treatment of the underlying delirium or other cause for agitation and aggression.

Recently we have shown that droperidol as a single agent is effective in sedation of adult patients in the emergency department, and was safer than benzodiazepines.[9] As part of an ongoing study of sedation in the emergency department we investigated the use of droperidol for sedation of elderly patients with ABD.

Methods

This was a prospective observational study of elderly patients (> 65 years of age) recruited as part of the DORM II study. DORM II is an observation study of patients with ABD presenting to an emergency department and requiring parenteral sedation and physical restraint. Ethics approval was obtained from the local Human Research Ethics Committee. Consent was waived because of the requirement for immediate treatment and the patients' lack of decision-making capacity to consent to medical treatment being given as a duty of care.

All adult patients (> 16 years of age) who present to the emergency department with ABD are recruited to DORM II if they do not calm with verbal de-escalation or oral medication, and require parenteral sedation and physical restraint. All patients are then treated according to a standardised intramuscular sedation and observation protocol in a critical care area.[9, 10] Heart rate (HR), blood pressure (BP), pulse oximetry and respiratory rate (RR) are recorded every 5 minutes for 20 minutes and thence every 30 minutes. Agitation and sedation are assessed using the sedation assessment tool (SAT; Figure 1).[11] The SAT score allows rapid assessment before and after sedative medication. The treatment protocol recommends an initial intramuscular dose of 10mg droperidol, followed by a second dose of 10mg if they are not sedated after 15 minutes. Patients not settling after 30 minutes must be discussed with the on call clinical toxicologist to determine any further sedation.[12]

An ABD chart is used to record all observations, adverse effects and treatments the patient receives. All patients have an electrocardiogram (ECG) done once settled. The QT interval is manually measured on all 12-lead ECGs, using a previously developed method.[13] QT-HR pairs from each ECG are plotted on the QT nomogram to determine if the QT is abnormal.[14] All information from the ABD chart and additional information from the medical record (e.g.

medication chart) is entered into a relational database, including demographics, medication used, sedation scores, clinical observations, QT interval and adverse effects.

We reviewed all emergency department patients with ABD who were 65 years and older from the DORM II database from August 2008 to August 2012. The following information was extracted: demographics, medication (time of dose, dose and additional sedation), time to sedation defined as a fall in the SAT score by two levels or a score of zero or less, failed sedation defined as not settling within two hours based on SAT scores, the proportion of patients requiring re-sedation after initially settling for at least one hour and adverse drug effects (RR < 12 breaths per min, systolic BP < 90mmHg, HR < 60bpm, oxygen saturation < 90, extrapyramidal side-effects or QT prolongation).

Medians, ranges and interquartile ranges (IQR) are reported for continuous variables. Percentages are reported for dichotomous outcomes with 95% confidence intervals (CI). Statistical and graphical analyses were done in GraphPad Prism version 5.03 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.

Results

There were 49 patients with a median age of 81 years (Range: 65 to 93y; IQR: 71 to 85y) and 33 were males (67%). Thirty of 49 patients (61%) were treated according to the recommended protocol and were initially administered 10mg droperidol. Seventeen patients were given less than the dose of droperidol recommended by the protocol – 5mg (15) and 2.5mg (2). Two other patients varied from the recommended drug protocol and were given midazolam (2.5mg and 5mg). Thirty four of the 49 patients had an ABD chart with the time to sedation completed, 22 of 30 receiving 10 mg droperidol, 10 of 15 receiving 5mg droperidol and the two receiving midazolam.

Three patients were not sedated within two hours. One patient was given 10mg droperidol, one was given 5mg droperidol, and a third was given 2.5mg midazolam. In those patients who were sedated, the median time to sedation in 21 of 30 receiving 10mg droperidol was 30 minutes (IQR: 18 to 40 min; Range 5 to 60 min) which compared to a median time to sedation of 21 minutes (IQR: 10 to 55 min; Range 5 to 108 min; p=0.55 Mann-Whitney) in 9 of 15 patients receiving 5mg droperidol (Figure 2). The patient who received 5mg midazolam took 50 minutes to sedate. Time to sedation was not recorded in 15 patients.

Eighteen patients (37%) required additional sedation (Figure 3), including 10 of 30 patients (33%; 95% CI: 18 to 53%) given 10mg droperidol compared to 7 of 15 patients (47%; 95% CI: 22 to 73%) given 5mg droperidol initially. One patient initially given 2.5mg midazolam required additional sedation. Fourteen patients (29%) required re-sedation more than 1 hour after their initial sedation, nine receiving 10mg droperidol initially, three receiving 5mg droperidol initially, one receiving 2.5mg droperidol and one receiving midazolam.

Adverse effects occurred in five patients (10%) – hypotension (2), over-sedation (2) and hypotension with over-sedation (1) (Table 1). One patient who developed hypotension (10mg

droperidol) had a myocardial infarction 12 hours after droperidol and died 2 weeks later. He was a 75 year old with pre-existing severe cardiac disease. Two of 30 patients (7%; 95%CI: 12 to 24%) given 10mg droperidol alone developed adverse effects compared to three of 19 patients (16%; 95% CI: 4 to 40%) who were not treated according to the sedation protocol (Table 1). Midazolam was administered to 5 patients on 10 occasions for initial or additional sedation. It was administered on a further 6 patients on 9 occasions for re-sedation. Midazolam was associated with two of the five adverse effects (Table 1), one patient given an initial dose and then further doses of midazolam and one given midazolam for additional sedation after droperidol. ECGs were obtained in 22 patients after droperidol and no patient had QT prolongation (Figure 4). There were no extrapyramidal side effects.

Discussion

This study shows that administering doses of 5 to 20mg of droperidol was effective in sedating the majority of elderly patients in the emergency department with ABD. The time to sedation was similar for patients initially given 5mg compared to those given 10mg. However, patients given an initial dose of 5mg were more likely to require an additional dose of droperidol to achieve sedation. Overall, 37 of the 49 patients (76%) were given a total of 10mg or more droperidol to initially achieve effective sedation (Figure 2 and 3). Adverse effects were uncommon, but appeared to be more common with a larger initial dose of droperidol and/or in combination with midazolam.

The study supports an initial lower or half dose of droperidol in the elderly with ABD, in line with previous reviews and guidelines[15-17]. However, further doses may need to be given after 15 minutes if the patient is not sedated.[4, 18] Incremental dosing gives the clinician the advantage of being able to judge the clinical effect over time, which is particularly useful in the elderly who have significant co-morbidities.

Traditionally haloperidol has been used as the first line drug for the treatment of ABD in the elderly.[19] It is thought to be safer than other drugs because it causes less sedation and respiratory depression, and has minimal effects on BP.[20] However, there are advantages to sedation in acutely agitated patients because it makes it easier to properly assess the patient and investigate underlying causes for the ABD[21]. Droperidol is more sedating than haloperidol, with a more rapid onset of action,[8] and has been shown to be effective for sedation of adult patients with ABD in the ED.[9, 22, 23]

Droperidol was issued with a black box warning by the FDA in 2001 because of concerns about QT prolongation and Torsades de Pointes (TdP).[24] However, a systematic review was unable to identify published cases of droperidol definitely causing TdP[25] and the spontaneous

reports to the FDA provided no clear evidence of an association between droperidol, TdP and death.[26] Prior to 2001, droperidol was used for decades specifically for severely agitated behavior and physical aggression with a good safety record.[27] There remains significant controversy in the literature regarding the validity of the evidence and if the FDA warning was warranted[25, 26, 28]. Our study suggests that droperidol is safe in the elderly with no cases of QT prolongation on ECGs collected after droperidol administration (Figure 4). Haloperidol was issued with a black box warning in 2007 with good evidence that it is associated with TdP.[29]

Adverse effects occurred in 10% of patients which is similar to studies of sedation in younger adult populations in the emergency department which report adverse effects in 13 to 19% of patients.[9 30, 31]. One 75 year old male patient had an acute myocardial infarction 12 hours after 10mg droperidol. He developed hypotension 30 minutes after being given droperidol, but the patient had a significant cardiac history and multiple factors were likely to be responsible for the poor outcome.

Midazolam was administered to 11 patients for initial, additional or re-sedation, despite it not being recommended as part of the DORM II protocol. It appeared to contribute to two of the five patients with adverse effects. This supports concerns with the use of benzodiazepines in the elderly, [6, 7] because they are known to cause delirium, excessive sedation, increased risk of falls, respiratory compromise and behavioral disinhibition.[16, 19]

All drugs used for rapid sedation are associated with adverse effects, and their use should always be a balance of the benefits in sedating patients with ABD versus the risks. Adverse effects occurred in two patients given 10mg droperidol alone and in another given 10 mg droperidol followed by midazolam (Table 1). This would suggest that a lower dose of 5mg initially may be the better option.

Conclusion

The study has shown that 5 to 10mg of droperidol is effective for sedating elderly patients in the emergency department with ABD. Adverse effects were uncommon and no more common than previous studies of adult populations. They appeared to occur with larger doses of droperidol and with midazolam alone or in combination with droperidol. A reasonable approach to sedating elderly patients with ABD would be to commence with 5mg droperidol with the expectation that repeat doses will be required in almost half of patients.

Declaration of Conflicting Interests

None declared.

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Table 1: Description of the adverse drug reactions, including the time of the reaction and the time and type of additional sedation administered.

Sex Age	Initial Drug (Dose; mg)	Adverse Effect		Additional Sedation	
		Type	Time (min)*	Time (min)*	Drug (Dose; mg)
M 75	Droperidol (10)	Hypotension	30	Nil	-
F 68	Droperidol (10)	Hypotension	5	Nil	-
M 73	Droperidol (10)	Airway Obstruction	100	40	Midazolam (10)
F 87	Droperidol (2.5)	Oversedation	480	270	Droperidol (2.5)
M 66	Midazolam (2.5)	Hypotension Oversedation	65/480	49 to 360	Midazolam (28) + Haloperidol (2.5)

* Time of adverse reaction or administration of additional sedation after the study drug was administered.

Table/Figure Legends

Table 1: Description of the adverse drug reactions, including the time of the reaction and the time and type of additional sedation administered.

Figure 1: Sedation Assessment Tool (SAT) used to assess the level of agitation and sedation in patients with acute behavioral disturbance.

Figure 2: Time to sedation for patients receiving 10mg droperidol (n=21) versus patients receiving 5mg droperidol (n=7).

Figure 3: Flow chart of the dose and drug used for initial and additional sedation.

Figure 4: Plot of QT versus HR for 22 patients given droperidol 10mg

Figure 1

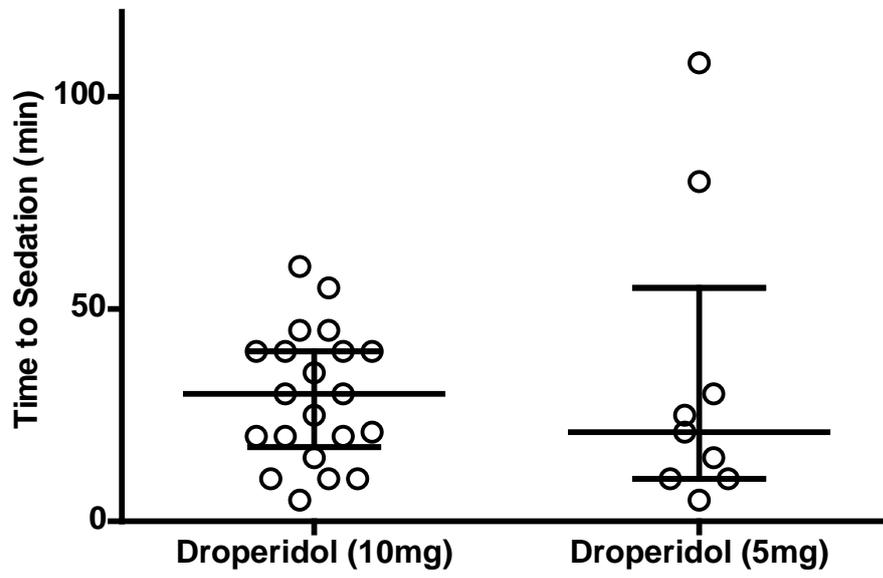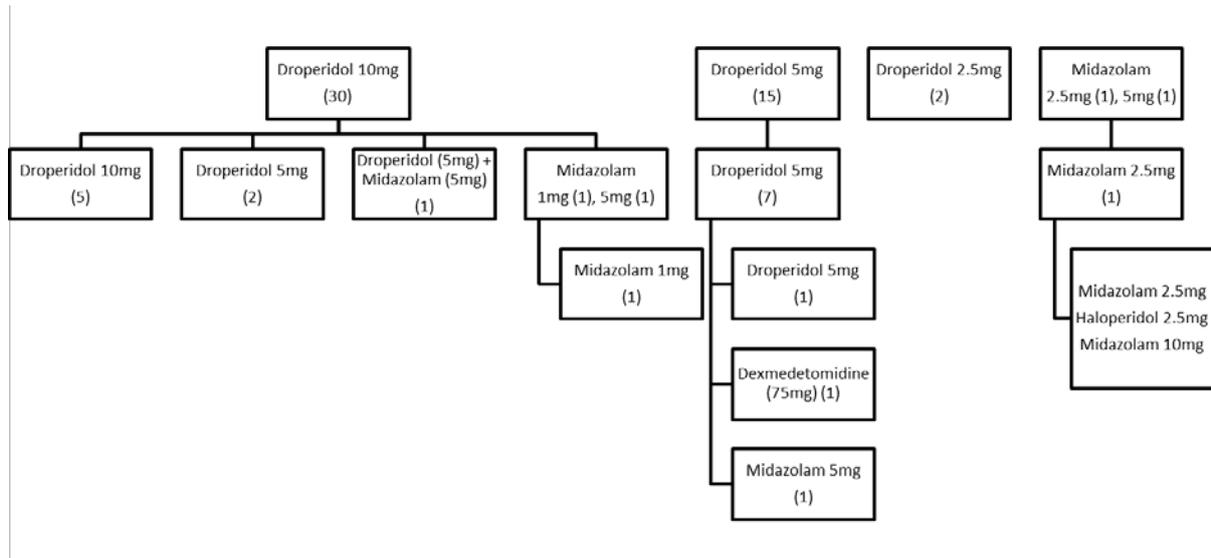| SCORE	RESPONSIVENESS	SPEECH
+3	Combative, violent, out of control	Continual loud outbursts
+2	Very anxious and agitated	Loud outbursts
+1	Anxious / restless	Normal / Talkative
0	Awake and calm / cooperative	Speaks Normally
-1	Asleep but rouses if name is called	Slurring or prominent slowing
-2	Responds to physical stimulation	Few recognisable words
-3	No response to stimulation	Nil

Figure 2

Figure 3

Figure 4