

The Safety and Effectiveness of Droperidol for Sedation of Acute Behavioral Disturbance in the Emergency Department

Leonie Calver; Colin B. Page, MBChB; Michael A. Downes, MBBS; Betty Chan, MBBS, PhD; Frances Kinnear, MBBS; Luke Wheatley, MBBS; David Spain, MBBS; Geoffrey Kennedy Isbister, MD, BSc*

*Corresponding Author. E-mail: geoff.isbister@gmail.com.

Study objective: We investigate the safety and effectiveness of droperidol for sedation of acute behavioral disturbance in the emergency department (ED).

Methods: This was a prospective observational study in 6 EDs (August 2009 to April 2013). Adult patients requiring parenteral sedation for acute behavioral disturbance received droperidol 10 mg. If this did not sedate the patient within 15 minutes, further sedation was allowed but droperidol 10 mg was recommended as part of a sedation protocol. The primary outcome was the proportion of patients with an abnormal QT interval, defined by the at-risk line on the QT nomogram. Secondary outcomes were effectiveness determined by the time to sedation measured on the Sedation Assessment Tool, use of additional sedation, adverse events, and injury to staff or patients.

Results: There were 1,009 patients with an ECG performed within 2 hours of droperidol administration, with a median dose of 10 mg (interquartile range [IQR] 10 to 17.5 mg). Thirteen of the 1,009 patients had an abnormal QT (1.3%; 95% confidence interval 0.7% to 2.3%), but 7 of these had another cause attributed for prolonged QT (methadone, escitalopram, amiodarone, or preexisting). In 1,403 patients sedated with a median total dose of droperidol of 10 mg (IQR 10 to 20 mg), the median time to sedation was 20 minutes (IQR 10 to 30 minutes) and 97% were sedated within 120 minutes. Additional sedation was required for 435 patients (31.0%; 95% confidence interval 28.6% to 33.5%). Adverse events occurred in 70 patients (5%) and oversedation without complications in 109 (8%), the latter more common for patients receiving benzodiazepines as additional sedation (16/109 [15%]). There were no cases of torsades de pointes. Injuries occurred in 34 staff members and 4 patients.

Conclusion: The study supports the use of high-dose droperidol as a safe sedating agent for patients with acute behavioral disturbance in the ED. There is no evidence of increased risk for QT prolongation with the doses used in this study. [Ann Emerg Med. 2015;■:1-9.]

Please see page XX for the Editor's Capsule Summary of this article.

0196-0644/\$-see front matter

Copyright © 2015 by the American College of Emergency Physicians.

<http://dx.doi.org/10.1016/j.annemergmed.2015.03.016>

SEE EDITORIAL, P. ■■■.

INTRODUCTION

Acute behavioral disturbance is a regular occurrence in emergency departments (EDs) worldwide, and it is disruptive and often dangerous for staff and patients. There are numerous causes of acute behavioral disturbance in the ED, the most common being drug and alcohol intoxication, mental illness, and deliberate self-harm.¹ The goal in the management of patients with acute behavioral disturbance is to ensure safety for the patient, staff, and other patients. When verbal de-escalation fails and oral medication is refused or ineffective, parenteral medication is the only option to sedate the patient to enable safe assessment, diagnosis, and treatment. All parenteral medication used for rapid sedation carries inherent risk,

and there is little consensus on which drug is optimal. The ideal drug would have a rapid onset and offset, and a low adverse event profile.² Benzodiazepines and antipsychotics, as single agents or in combination, have been the 2 major drug groups used for sedating patients with acute behavioral disturbance. The lack of consensus has led to vastly differing clinical practice, with potentially dangerous cumulative doses being administered and high adverse event rates.³

Droperidol is a sedating first-generation antipsychotic that has been used to safely treat acute behavioral disturbance for decades.^{4,5} A controversial decision was made by the Food and Drug Administration to publish a black box warning for droperidol⁶ in December 2001 because of reported cases of QT prolongation and torsades de pointes. The black box warning has led to a marked

Editor's Capsule Summary*What is already known on this topic*

Although previously popular, the emergency department (ED) administration of droperidol substantially waned after the Food and Drug Administration issued a controversial black box warning in 2001 about potential QT prolongation.

What question this study addressed

Does high-dose droperidol cause QT prolongation or torsades de pointes?

What this study adds to our knowledge

In this observational study of 1,009 ED adults receiving a median of 10 mg of droperidol for acute behavioral disturbance, QT prolongation was observed in just 1.3%, of whom half had other reasons for such prolongation. There were no cases of torsades de pointes or other serious adverse events.

How this is relevant to clinical practice

Droperidol is safe even with the high doses used in this study.

reduction in the use of droperidol around the world despite a systematic review⁷ and increasing evidence that the risk of QT prolongation with droperidol is minimal.^{4,8} A number of more recent studies have demonstrated that droperidol is at least as effective as benzodiazepines in sedating patients with acute behavioral disturbance and is potentially safer.^{8,9}

Goal of This Investigation

This study aimed to investigate the frequency of QT prolongation and torsades de pointes in patients administered high-dose (10 mg or more) droperidol in the ED for acute behavioral disturbance. In addition, it aimed to investigate the frequency of other adverse events and the effectiveness of droperidol for sedation.

MATERIALS AND METHODS**Study Design and Setting**

This was a prospective multicenter observational study of patients administered droperidol for sedation of acute behavioral disturbance in the ED, including the recording of an ECG within 2 hours of drug administration. The study was undertaken in 6 large regional and metropolitan EDs between August 2009 and March 2013. The hospitals

ranged in size and case mix and included those in large cities, as well as large urban regional hospitals. Ethics approval was obtained from the Hunter New England Area Health Service Human Research Ethics Committee to cover 2 hospital sites in New South Wales and from the Princess Alexandra Human Research Ethics Committee to cover 4 hospitals in Queensland. Consent was waived because of the requirement for immediate treatment and patients' inability to consent to a study because medical treatment was being given as a duty of care without consent. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN 12611000031965). Data collection commenced immediately after the completion of a randomized controlled trial of droperidol (the Droperidol or Midazolam [DORM] study) in one of the participating hospitals.⁸

Selection of Participants

ED patients were eligible to be included if they had acute behavioral disturbance, were at risk to themselves or others, and had a score of 2 to 3 on the Sedation Assessment Tool (Figure E1, available online at <http://www.annemergmed.com>).¹⁰ The Sedation Assessment Tool score is used routinely in all the study EDs to assess the degree of agitation and depth of sedation, with a score of 3 (physically violent) to -3 (unconscious). Patients were excluded if they were willing to receive oral medication for sedation or were younger than 18 years. Inclusion of patients was determined by the ED staff, and in some cases patients scored only 1 on the Sedation Assessment Tool score but required parenteral sedation to prevent their leaving or to have appropriate medical investigation and treatment as a duty of care.

Interventions

A protocol was introduced into each ED for the sedation of patients with acute behavioral disturbance that included the administration of high-dose droperidol (10 to 20 mg) and the use of the Sedation Assessment Tool to determine the effectiveness and safety of sedation (Figure E2, available online at <http://www.annemergmed.com>). The 10-mg initial dose was based on a previous randomized controlled trial.⁸ Patients with acute behavioral disturbance meeting the inclusion criteria were physically restrained and administered 10 mg of droperidol either intramuscularly in the thigh or deltoid muscle or intravenously if a cannula had previously been inserted. If the patient did not settle (ie, Sedation Assessment Tool score decreased by 2 or returned to zero) within 15 minutes, an additional dose of droperidol 10 mg was recommended. After 20 mg of

droperidol had been administered, additional droperidol or other medications were given at the discretion of the treating physicians. Droperidol was available in vials of 10 mg/2 mL concentration (DORM), which enabled 10 mg to be given with a single injection. This formulation of droperidol (DORM) was manufactured (Phebra Pty Ltd, Sydney, New South Wales, Australia) in a pharmaceutical manufacturing facility approved by the Therapeutic Goods Administration in Australia and was provided under schedule 5A-subregulation 12(1A) of the Therapeutic Goods Act and Regulation, Australia. This was an observational study of a clinical protocol in which droperidol was administered, and not a clinical trial, so the use of droperidol was according to the schedule 5A, which relates to clinical use of drugs, and a clinical trials notification was therefore not required.

All patients were initially treated in a critical care area of the ED. They were attached to a cardiac monitor, pulse oximetry, and noninvasive blood pressure machine as soon as they were settled enough. Sedation Assessment Tool scores and vital signs were recorded every 5 minutes from the initial or subsequent doses of droperidol for 20 minutes and then half-hourly. Vital signs, including heart rate (HR), blood pressure, oxygen saturation, and respiratory rate, were ticked on the acute behavioral disturbance data sheet to indicate they were within normal range or recorded numerically if they were abnormal. ECGs were obtained as soon as practical after the patient was sufficiently settled and compliant.

Data Collection and Processing

All data were recorded on a purpose-designed acute behavioral disturbance observation form (Figure E2, available online at <http://www.annemergmed.com>), which was part of the medical record and used for research data collection. All acute behavioral disturbance data forms and ECGs were de-identified and then faxed to a confidential fax number from each hospital to the chief investigator (L.C.) at the lead site. The acute behavioral disturbance data forms contained demographic information (age and sex), reason for ED presentation, details of drug administration (time and dose), sedation scores, vital signs (HR, blood pressure, oxygen saturation, and respiratory rate), any adverse events, and staff injuries. Data were extracted from the acute behavioral disturbance forms and entered into a relational database (Microsoft Access; Microsoft, Redmond, WA).

ECGs were included only if they were conducted within 2 hours of droperidol administration. The QT interval was manually measured on each ECG with a previously developed method.^{11,12} In brief, the QT was measured manually in 3 limb leads and 3 chest leads and the median

was taken. HR was taken from the ECG. All ECGs were read by 1 investigator (L.C.), and, to ensure good agreement, a subset of 100 was reviewed by another investigator (C.B.P.), with 86% within 20 ms of one another and 96% agreement for their being normal or abnormal according to the QT nomogram. ECGs were excluded if the HR was greater than 150 beats/min because the QT is difficult or impossible to measure at extreme HR and in the evaluation of the nomogram the fastest HR for drug-induced torsades de pointes was 146 beats/min.¹³ The QT was plotted against the HR on the QT nomogram.^{11,13} If it was above the “at-risk line,” it was considered abnormal.

The QT nomogram was used in preference to HR correction formulae and a particular QTc cutoff because all HR correction formulae are prone to overcorrecting the QT for fast HRs and undercorrecting it for slow ones.^{11,14} This is most problematic for Bazett’s correction (QTcB), which is accurate only for HRs between 50 and 70 beats/min. The QT nomogram has been evaluated in a systematic review of cases of drug-induced torsades de pointes versus a control group of overdose patients receiving noncardiotoxic drugs and shown to be more sensitive and specific than Bazett’s HR correction, with cutoffs at 440 and 500 ms.¹³ The QT nomogram has been used for assessment of the risk of QT prolongation in drug overdose patients.^{11,14,15}

Outcome Measures

The primary outcome was the proportion of patients who had an abnormal QT, defined as the QT–HR pair’s being above the “at-risk” line on the QT nomogram in a 2-hour period after the last droperidol administration (ie, either after the initial dose if only a single dose was given or after the last additional dose of droperidol). The secondary outcomes were the proportion of patients with torsades de pointes, other adverse events, time to sedation, failed sedation, requirement for additional sedation, oversedation (Sedation Assessment Tool score –3), and staff injuries. The time to sedation was defined as the time from the initial dose of droperidol until the Sedation Assessment Tool score decreased by 2 points or more or the score was zero (awake and calm) (Sedation Assessment Tool; Figure E1, available online at <http://www.annemergmed.com>). Failed sedation was defined as patients not sedated within 120 minutes (ie, a Sedation Assessment Tool score was not recorded with a reduction of 2 levels or a return to zero). The requirement for additional sedation was defined as any medication administered for the purpose of sedation within 60 minutes of the initial droperidol dose. Adverse drug events were defined as any new-onset arrhythmia including torsades de pointes, oxygen saturation less than

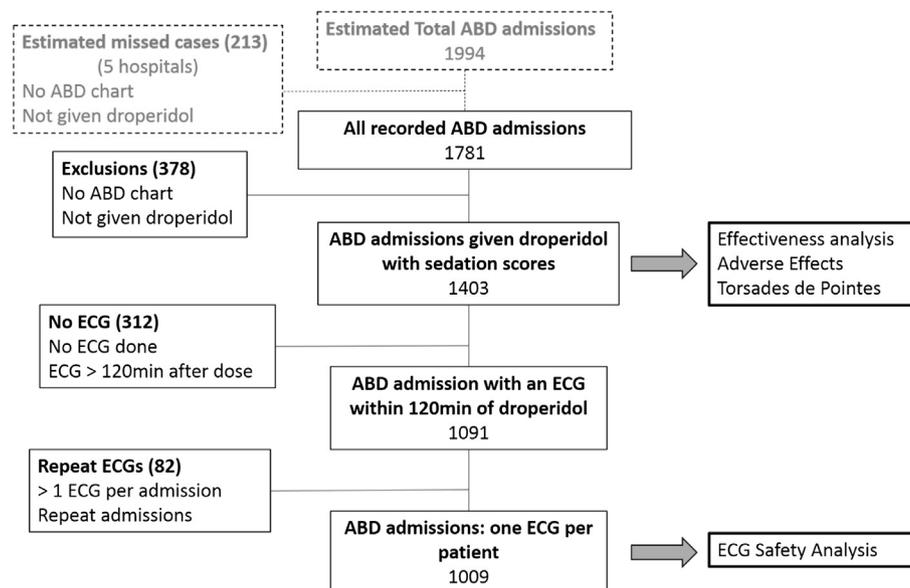


Figure 1. Flow chart of the patients recruited, excluded patients, and the 2 cohorts of patients included in the final analysis. ABD, Acute behavioral disturbance; ECG, electrocardiogram.

90%, airway obstruction, systolic blood pressure less than 90 mm Hg, and respiratory rate less than 12 breaths/min.

Primary Data Analysis

The sample size for the study was based on demonstrating that the incidence of QT prolongation and torsades de pointes is rare and QT prolongation occurs in no more than 0.5% of patients. Assuming that an abnormal QT does not occur in the study, we would need 950 patients to be confident (97.5% confidence interval [CI]) that an abnormal QT occurs in less than 0.5% of patients. This is calculated as the 95% CI around a proportion of no events in 950 patients (0/950), using the Wilson procedure with continuity correction. We aimed to recruit 1,000 patients, assuming that ECGs might not be conducted in 5% of them.

Medians and interquartile ranges, 95th percentiles, or ranges are reported for continuous variables, and dichotomous variables are reported as percentages with 95% CI, using the Wilson procedure with continuity correction. The primary outcome was presented as a proportion with 95% CI. All analyses and graphics were conducted with GraphPad Prism (version 6.03; GraphPad Software, San Diego, CA).

RESULTS

There were 1,781 patient presentations reported to the investigators from the 6 EDs for acute behavioral disturbance between August 2009 and March 2014, with a median of 164 per hospital (52 to 928). There were 1,403

of 1,781 presentations with a complete set of data collected, including when droperidol was the initial drug given and there was a completed acute behavioral disturbance chart and a time to sedation recorded. There were no cases of torsades de pointes in these excluded patients. In the hospital recruiting the largest number of patients (928 of 1,781 [52%]), there was close to 100% capture of acute behavioral disturbance cases in which parenteral sedation was administered because the security log was reviewed weekly and droperidol use was closely monitored by the pharmacy. In this hospital, only 653 of 928 patients (70%) were included in the sedation cohort compared with a median of 87% (Range: 83% to 91%) in the other 5 hospitals, indicating that there were cases missed at the other hospitals for which no information was faxed. By correcting for the difference between inclusion rates of each hospital compared with that of the first hospital, we estimate that 213 patients were missed at the other sites and not recorded, making the estimated total 1,994 (Figure 1). Review of the excluded cases at the first hospital indicated that staff being too busy to fill out charts and new junior staff preferentially using another drug were the main reasons for exclusion. No cases were excluded where droperidol was given and there was an adverse event, and there were no cases of torsades de pointes.

The cohort of 1,403 patients was used to assess the effectiveness of droperidol for sedation and adverse events. In 1,091 admissions, there was at least 1 ECG conducted within 120 minutes, excluding multiple ECGs and multiple admissions for the same patient, and ECGs with a HR greater than 150 beats/min. From this, there were

Table 1. Baseline characteristics of the 2 cohorts of patients.

Demographics/Characteristics	Effectiveness Cohort			QT Cohort		
	Number	%	N=1,403	Number	%	N=1,009
Age, median (IQR), y	34 (25–44)		1,391	34 (25–43)		999
Men (%)	840	59.9	1,403	631	62.5	1,009
Reason for presentation						
Alcohol intoxication*	609	52.6	1,157	421	50.6	832
Deliberate or threatened self-harm	287	24.8	1,157	200	24.0	832
Psychostimulants	160	13.8	1,157	130	15.6	832
Mental illness/psychosis	182	15.7	1,157	142	17.1	832
Head injury	16	1.4	1,157	12	1.4	832
Medical cause	30	2.6	1,157	10	1.2	832
Other	56	4.8	1,157	25	3.0	832
Blood alcohol level, median (IQR), mg/dL	0.23 (0.18–0.28)		278	0.22 (0.18–0.28)		
Previous sedation [†]	67	4.8	1,403	49	4.9	1,009
Baseline Sedation Assessment Tool scores						
3	827	61.9	1,335			
2	473	35.4	1,335			
1	35	2.6	1,335			
Initial droperidol dose, median (95th percentile), mg	10 (10–10)			10 (10–10)		

*Patients with alcohol intoxication could also have another reason for presentation.

[†]Sedation given in the hours before parenteral droperidol, usually before the hospital.

1,009 single patient admissions included in the ECG safety analysis (Figure 1). The HR was greater than 150 beats/min in only 3 patients who were excluded. The demographic details for each cohort are included in Table 1 and were similar among the hospitals.

The median total dose of droperidol given before the first ECG in the 1,009 patients was 10 mg (interquartile range 10 to 17.5 mg). In these 1,009 ECGs from single patients, the median QT was 360 ms (95th percentile 320 to 440 ms). Thirteen of the 1,009 patients had an abnormal QT (1.3%; 95% CI 0.7% to 2.3%), which is shown on the QT nomogram (Figure 2). The number of cases of an abnormal QT for each hospital is included in Table E1, available online at <http://www.annemergmed.com>. Of the 13 patients with abnormal QTs, 2 had preexisting abnormal QT according to ECGs before or after the administration of droperidol, 2 were receiving methadone, 2 were receiving escitalopram, and 1 was receiving amiodarone, all drugs associated with QT prolongation (Figure 2). Excluding patients with another reason for a prolonged QT interval, there were only 6 patients (0.6%; 95% CI 0.2% to 1.4%) with an abnormal QT. There were no cases of torsades de pointes. There were 33 elderly patients (age ≥ 65 years; 3.3%) who had a median QT of 390 ms (95th percentiles 320 to 448 ms), which was slightly longer than that of all patients (Table E2, available online at <http://www.annemergmed.com>).

The median initial dose of droperidol in the 1,403 patients was 10 mg (95th percentile 10 to 10 mg; range 2.5 to 20 mg) and the median total dose was 10 mg (95th percentile 10 to 20 mg; range 2.5 to 40 mg). The median

time to sedation in the 1,403 patients was 20 minutes (interquartile range 10 to 30 minutes; range 2 to 120 minutes). There were 1,354 patients (97%) sedated within 120 minutes and 49 patients who failed sedation (Figure 3). The initial dose of droperidol effectively sedated 968 patients (69.0%; 95% CI 66.5% to 71.4%) and

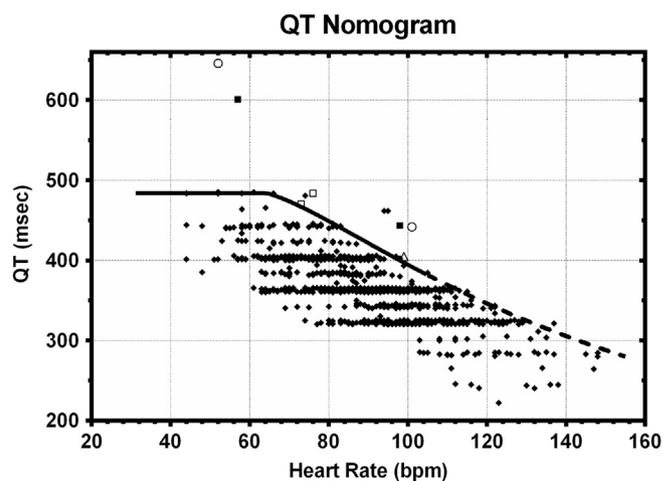


Figure 2. QT nomogram with plots of QT/HR pairs (black filled circles) below and above the “at-risk” line (black line). The QT nomogram is used for determining whether a QT interval is at risk from a single 12-lead ECG (modified from Figure 1 of Fossa et al²¹). The at-risk line is a close approximation of the figure and the dashed section is extrapolated for faster HRs.¹³ Two patients had abnormal QT before receiving droperidol (open circles), 2 patients were receiving methadone (filled squares), 2 patients were receiving escitalopram (open squares), and 1 patient was receiving amiodarone (open triangle).

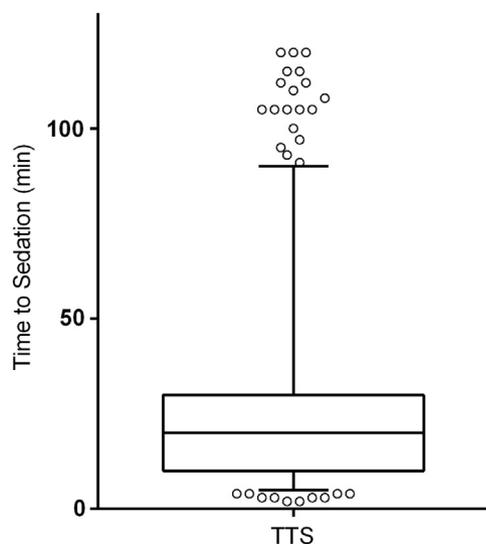


Figure 3. Box-and-whiskers plot of the times of sedation for the 1,354 patients who sedated within 120 minutes. The whiskers are 5th and 95th percentile, the box is interquartile range, and open circles are outliers. The 49 patients not sedated within 120 minutes are not included on the plot but are included in the calculation of the median, percentiles, and ranges. TTS, Time to sedation.

additional sedation was required for 435 patients (31.0%; 95% CI 28.6% to 33.5%), although droperidol was not used in all cases of additional sedation. Of these 435 patients, 323 (23.0%) had 1 further dose, 70 (5.0%) 2 further doses, 28 (2.0%) 3 further doses, and 14 (1.0%) 4 or more additional doses. Droperidol alone was given to 299 of the 435 patients who had additional sedation. Additional sedation was used more often for patients given a lower initial dose, 26 of 61 (42.6%; 95% CI 30.3% to 55.9%) given 5 mg compared with 405 of 1,337 (30.3%; 95% CI 27.9% to 32.8%). Only 3 patients were given 2.5 mg as an initial dose, and 2 required additional sedation.

Oversedation (Sedation Assessment Tool score -3 , equivalent to U on the AVPU score) occurred in 109 patients (7.8%). Benzodiazepines were given for 16 of the 109 patients (15%) who were oversedated compared with only 82 of 1,294 patients (6.3%) who were not. Table 2 shows that 3 or more additional sedations and the use of benzodiazepines are associated with oversedation. Elderly patients ($N=61$; 4.3%) had a slightly longer time to sedation (median 25 minutes) and larger requirement for additional sedation (43%) (Table E2, available online at <http://www.annemergmed.com>).

There were 71 adverse events in 70 patients (70/1,403 [5.0%]; 95% CI 3.9% to 6.3%), with 1 patient having 2 adverse events (airway obstruction and desaturation). The number of each of the adverse events is shown in Table 3, with the commonest being hypotension (28 patients) and

desaturation (22 patients). Of the 8 patients with airway obstruction, 6 required a nasopharyngeal airway or jaw thrust briefly, 1 was repositioned on the side, and 1 was intubated but had taken a tricyclic antidepressant overdose. Only 2 of the 8 received 10 mg droperidol alone, 3 received benzodiazepines before droperidol (out-of-hospital), 2 had sedative overdoses, and 1 was given 30 mg droperidol and 200 mg ketamine. Eleven of the 22 patients with desaturation had oxygen applied and 3 were stimulated or had jaw thrust. Table 2 shows that additional sedation or sedation with benzodiazepines was not associated with increased adverse events except oversedation. One patient had a cardiac history and developed atrial flutter that resolved.

There was no difference in the total dose given to patients who had adverse events compared with those who did not. The 98 patients given benzodiazepines (midazolam or diazepam) in addition to droperidol had similar numbers of adverse effects compared to the 1305 given droperidol alone (4/98 [4.1%] versus 66/1305 [5.1%]). Injuries were reported in 38 admissions (2.7%), including 34 staff injuries (punches [13], kicks [4], bites [2], spitting [6], scratches [2], needle stick injury [1], and unknown [6]) and 4 patient injuries. There were 4 adverse events in 61 elderly patients, which was similar to those of all patients (Table E2, available online at <http://www.annemergmed.com>).

LIMITATIONS

A limitation of the study was the difficulty obtaining ECGs at the same time for every patient, and many ECGs could not be done within the 2-hour timeframe of administration of droperidol. Patients were either uncooperative or staff were reluctant to disturb them once they were settled. However, more than 1,000 ECGs were conducted within 2 hours of droperidol administration, and this is when the peak effects of droperidol are likely to occur. Despite the large number of ECGs, the study was still unable to rule out rare adverse events ($<0.1\%$): torsades de pointes. The rarity of torsades de pointes means that much larger studies are required to show that there is no or minimal association between droperidol and torsades de pointes.

A second limitation of the study was that in only 1 hospital was the data collection completely consecutive. We estimated that approximately 213 patients were missed at the other 5 sites. Although there is a small likelihood of bias being introduced because potentially a proportion of clinicians avoided droperidol, this avoidance did not appear to be based on particular patient characteristics and, when

Table 2. Number of patients given additional sedation, including the number of additional sedations and drugs given, the proportion with adverse events, and the proportion with oversedation.

Drug Given	Number	Adverse Events	%	Oversedation	%
All patients	1,403	70	5.0	109	7.8
Single droperidol dose, mg	968	45	4.6	73	7.5
10	933	43	4.6	72	7.7
5	35	2	5.7	1	2.9
All additional sedation patients	435	25	5.7	36	8.3
Additional sedation, 1 dose	323	18	5.6	25	7.7
Two droperidol doses	280	16	5.7	18	6.4
Droperidol+benzodiazepine	40	2	5.0	7	18
Droperidol+midazolam	33	1	3.0	5	12
Droperidol+diazepam	7	1	14.3	2	29
Droperidol+other (1 add)	3	0	—	0	—
Additional sedation, 2 doses	70	4	5.7	5	7.1
3 droperidol doses	15	0	—	1	6.7
Droperidol+2 other drugs	55	4	7.3	4	7.3
Droperidol (×2)+midazolam	17	2	11.8	1	5.9
Droperidol (×2)+diazepam	8	0	—	2	25
Droperidol (×2)+ketamine	20	1	5.0	0	—
Droperidol (×1)+benzodiazepine (×2)	7	0	—	1	14
Droperidol (×2)+dexmedetomidine	1	1	100	0	—
Droperidol (×2)+other*	2	0	—	0	—
Additional sedation, 3 doses	28	2	7.1	4	14
4 droperidol doses	4	0	—	0	—
Droperidol+3 other drugs	24	2	8.3	4	17
Droperidol (×2)+midazolam (×2)	8	0	—	3	38
Droperidol (×3)+midazolam	3	0	—	0	—
Droperidol (×3)+ketamine	7	1	14	0	—
Other combinations†	6	1	17	1	17
Additional sedation, 4 or more doses	14	1	7.1	2	14
Droperidol+benzodiazepines	7	0	—	1	14
Droperidol+benzodiazepines+dexmedetomidine	4	0	—	1	25
Droperidol (×3)+dexmedetomidine	1	1	100	0	—
Droperidol+ketamine	2	0	—	0	—
Additional sedation includes a benzodiazepine	98	4	4.1	16	15
Additional sedation only droperidol	299	16	5.4	19	6.4
All patients not given a benzodiazepine	1,305	66	5.1	93	7.1

—, No cases.

*One patient was given haloperidol and 1 patient was intubated for agitation/aggression.

†One patient had an adverse event with dexmedetomidine and another had oversedation with zuclopenthixol.

reviewed at one hospital, was mainly because of junior staff unfamiliar with droperidol.

Another limitation was that not all the demographic and baseline data were available for all patients because the information on the acute behavioral disturbance observation form was incomplete in a small number of cases. The investigators relied on the treating team to fill out the form and fax it back. However, state laws required that all information faxed across borders be deidentified, so the investigators were unable to double check this information once patients had been discharged. Less than 5% of the baseline data were missing and this did not affect the study outcomes.

The study was conducted in the setting of the ED with patients who could not be settled with verbal de-escalation or oral sedation. A limitation of this is that the

results cannot be generalized to other settings such as the acute psychiatric setting, where mental illness is far more prevalent, or general medical or drug and alcohol withdrawal patients. One recent study in a psychiatric

Table 3. Number of the different adverse events and the proportion in the total cohort.

Adverse Event	No.	%
Desaturation (<90%)	22*	1.6
Airway obstruction	8	0.6
Hypotension	28	2.0
Extrapyramidal adverse events	7	0.5
Arrhythmia	1	0.1
Hypoventilation (respiratory rate <12 breaths/min)	4	0.2
Seizure	1	0.1
No adverse events	1,333	95

*One patient had both airway obstruction and desaturation.

ICU demonstrated that droperidol and haloperidol were safe and equally effective in sedating agitated and aggressive patients.¹⁶ Further studies are required in different patient groups to establish the safety and effectiveness of droperidol.

DISCUSSION

This study has shown that an abnormal QT interval is rare in a large cohort of patients given high-dose droperidol. In addition, there were no cases of torsades de pointes in the larger cohort of 1,403 patients, suggesting that the risk of torsades de pointes is less than 0.3% according to the size of the cohort. In addition, the study showed that droperidol was effective for sedation, with almost all patients being sedated within 120 minutes and less than a third requiring 2 or more doses. Adverse events occurred in 5% of patients, and oversedation with a Sedation Assessment Tool score of -3 occurred in 8% but did not require any specific intervention. Oversedation was more common in patients given additional benzodiazepines and in patients requiring additional sedation on 3 or more occasions. The study demonstrates that high-dose droperidol appears to be relatively safe and effective for sedation of acute behavioral disturbance in the ED. Initial doses of less than 10 mg were associated with the requirement for additional sedation.

The frequency of abnormal QT intervals was 1.3% (95% CI 0.7% to 2.3%), which was not significantly different to that observed in the control group of patients used to evaluate the QT nomogram, 1.3% (95% CI 0.4% to 3.4%).¹³ In half of the patients with an abnormal QT, there was another clear cause for it, including known QT-prolonging drugs (eg, methadone) or preexisting QT prolongation. This and the absence of torsades de pointes suggest that droperidol in doses of 10 to 20 mg is highly unlikely to cause QT prolongation and patients do not need routine ECGs after receiving droperidol. This is consistent with results of smaller randomized controlled trials of droperidol, which also did not demonstrate QT prolongation as a problem.^{8,9,17}

The goal of effective sedation is rousable sleep, not unconsciousness.² In this study, only 109 of the 1,403 patients (7.8%) had a sedation score of -3 , and thus greater than 90% were either easily roused or roused to physical stimuli. This had been identified in the previous DORM study, which showed that patients given droperidol were rarely oversedated.⁸ Patients who were given midazolam or diazepam as part of their additional sedation were at least twice as likely to develop oversedation (Table 2). This association of benzodiazepines with oversedation has been shown in previous studies.^{8,18,19} This supports concerns

about the use of benzodiazepines for sedation of patients with acute behavioral disturbance. To our knowledge, no study has shown significant benefit of benzodiazepines over droperidol in the sedation of this patient group.^{8,9,19,20} Knott et al⁹ reported only a median difference in the time to sedation of 1.5 minutes when midazolam was given intravenously compared with droperidol, and there was no difference between midazolam and droperidol in the DORM study.⁸ Oversedation was also associated with 3 or more attempts at additional sedation, although not when droperidol was the only agent used (Table 2). This suggests that sedation with combinations of agents, particularly benzodiazepines, should be avoided.

This study has shown that droperidol is relatively safe and effective for the management of violent and aggressive patients in the ED and that there was no increased risk of QT prolongation and torsades de pointes according to a large cohort of cases. Very large studies are required to completely rule out any risk of QT prolongation and torsades de pointes. The study also supports concerns about the increased oversedation and adverse events associated with the addition of a benzodiazepine to droperidol.

The authors acknowledge Calvary Mater Emergency Department staff and Angela Chiew, MBBS, at ED Prince of Wales Hospital.

Supervising editor: Steven M. Green, MD

Author affiliations: From the School of Medicine and Public Health, University of Newcastle, New South Wales, Australia (Isbister, Calver); the Emergency Department, Princess Alexandra Hospital, Queensland, and the School of Medicine, University of Queensland, Brisbane, Australia (Page); the Emergency Department, Calvary Mater Newcastle, Newcastle, New South Wales, Australia (Isbister, Downes); the Emergency Department, Prince of Wales Hospital, Sydney, New South Wales, Australia (Chan); the Prince Charles Hospital, Brisbane, Queensland, Australia (Kinneary); the Cairns Base Hospital, Cairns, Queensland, Australia (Wheatley); and the Gold Coast and Robina Hospitals, Gold Coast, Queensland, Australia (Spain).

Author contributions: GKI and LC designed the study. LC and CBP enlisted the additional sites. LC supervised the study and entered the data. CBP, MAD, BC, FK, LW, and DS recruited or supervised recruitment of patients and data collection. GKI performed a data audit and analyzed the data. LC wrote the first draft and all authors contributed to the final article. GKI takes responsibility for the paper as a whole.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist and provided the following details: Dr. Isbister is supported by NHMRC Senior Research Fellowship

1061041. The study was funded in part by NSW Health Drug and Alcohol Research Grants Program 2010.

Publication dates: Received for publication January 7, 2015.

Revisions received February 10, 2015; and March 12, 2015.

Accepted for publication March 16, 2015.

REFERENCES

- Downes MA, Healy P, Page CB, et al. Structured team approach to the agitated patient in the emergency department. *Emerg Med Australas*. 2009;21:196-202.
- National Institute of Clinical Excellence. *Violence: The Short Term Management of Disturbed/Violent Behaviour in Inpatient Psychiatric Settings and Emergency Departments*. Clinical Guidelines. London, England: NICE; 2005.
- Calver L, Drinkwater V, Isbister GK. A prospective study of high dose sedation for rapid tranquilisation of acute behavioural disturbance in an acute mental health unit. *BMC Psychiatry*. 2013;13:225.
- Chase PB, Biros MH. A retrospective review of the use and safety of droperidol in a large, high-risk, inner-city emergency department patient population. *Acad Emerg Med*. 2002;9:1402-1410.
- Powney MJ, Adams CE, Jones H. Haloperidol for psychosis-induced aggression or agitation (rapid tranquilisation). *Cochrane Database Syst Rev*. 2012;(11):CD009377.
- Horowitz BZ, Bizovi K, Moreno R. Droperidol—behind the black box warning. *Acad Emerg Med*. 2002;9:615-618.
- Kao LW, Kirk MA, Evers SJ, et al. Droperidol, QT prolongation, and sudden death: what is the evidence? *Ann Emerg Med*. 2003;41:546-558.
- Isbister GK, Calver LA, Page CB, et al. Randomized controlled trial of intramuscular droperidol versus midazolam for violence and acute behavioral disturbance: the DORM study. *Ann Emerg Med*. 2010;56:392-401.e1.
- Knott JC, Taylor DM, Castle DJ. Randomized clinical trial comparing intravenous midazolam and droperidol for sedation of the acutely agitated patient in the emergency department. *Ann Emerg Med*. 2006;47:61-67.
- Calver LA, Stokes B, Isbister GK. Sedation assessment tool to score acute behavioural disturbance in the emergency department. *Emerg Med Australas*. 2011;23:732-740.
- Isbister GK, Page CB. Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice. *Br J Clin Pharmacol*. 2013;76:48-57.
- Isbister GK, Calver L, van Gorp F, et al. Inter-rater reliability of manual QT measurement and prediction of abnormal QT,HR pairs. *Clin Toxicol (Phila)*. 2009;47:884-888.
- Chan A, Isbister GK, Kirkpatrick CM, et al. Drug-induced QT prolongation and torsades de pointes: evaluation of a QT nomogram. *QJM*. 2007;100:609-615.
- Isbister GK. How do we assess whether the QT interval is abnormal: myths, formulae and fixed opinion. *Clin Toxicol (Phila)*. 2015; In press.
- Berling I, Isbister GK. Prolonged QT risk assessment in antipsychotic overdose using the QT nomogram. *Ann Emerg Med*. 2015. <http://dx.doi.org/10.1016/j.annemergmed.2014.12.005>.
- Calver L, Drinkwater V, Gupta R, et al. Droperidol v. haloperidol for sedation of aggressive behaviour in acute mental health: randomised controlled trial. *Br J Psychiatry*. 2015;206:223-228.
- Chan EW, Taylor DM, Knott JC, et al. Intravenous droperidol or olanzapine as an adjunct to midazolam for the acutely agitated patient: a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Ann Emerg Med*. 2013;61:72-81.
- Spain D, Crilly J, Whyte I, et al. Safety and effectiveness of high-dose midazolam for severe behavioural disturbance in an emergency department with suspected psychostimulant-affected patients. *Emerg Med Australas*. 2008;20:112-120.
- Martel M, Sterzinger A, Miner J, et al. Management of acute undifferentiated agitation in the emergency department: a randomized double-blind trial of droperidol, ziprasidone, and midazolam. *Acad Emerg Med*. 2005;12:1167-1172.
- Richards JR, Derlet RW, Duncan DR. Chemical restraint for the agitated patient in the emergency department: lorazepam versus droperidol. *J Emerg Med*. 1998;16:567-573.
- Fossa AA, Wisialowski T, Magnano A, et al. Dynamic beat-to-beat modeling of the QT-RR interval relationship: analysis of QT prolongation during alterations of autonomic state versus human ether a-go-go-related gene inhibition. *J Pharmacol Exp Ther*. 2005;312:1-11.

APPENDIX

Table E1. The number of patients with an abnormal QT for each hospital, including the proportion with 95% CIs.

Hospital	Number of ECGs	Abnormal QT	Proportion, %	95% CI
1	67	0	0	0–6.8
2	389	8	2.10	1.0–4.2
3	35	0	0	0–12.3
4	296	4	1.40	0.4–3.7
5	138	1	0.70	0–4.6
6	84	0	0	0–5.5

Figure E1. Sedation Assessment Tool.

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 recognizable words
–3	No response to stimulation	None

Table E2. Demographics, baseline characteristics, and outcomes for elderly patients (>65 years) compared with the whole cohort.

Demographics/Characteristics	Effectiveness Cohort, Elderly	%, N = 61	Effectiveness Cohort, All	%, N = 1,403	QT Cohort, Elderly	%, N = 33	QT Cohort, All	%, N = 1,009
Age, median (range), y	75 (65–93)		34 (25–44)		74 (65–93)		34 (25–43)	
Men, %	43	70	840	60	24	73	631	63
Droperidol dose, median (95% PI), mg	10 (5–10)		10 (10–10)		10 (10–10)		10 (10–10)	
QT, median (95th percentile), ms					390 (320–448)		360 (320–440)	
Time to sedation, median (IQR)	25 (12–37)		19 (10–30)					
Sedated within 120 min	54	89	1,354	97				
Additional sedation, %	26	43	453	32				
Adverse events, %	4	7	71	5				

PI, Percentile.