

Study full title: An audit of a change in clinical practice for Queensland Ambulance Service from midazolam to droperidol for prehospital acute behavioural disturbance.

Study short title: Audit of acute behavioural disturbance management.

Summary:

Acute behavioural disturbance (ABD) from alcohol, amphetamines, other stimulants, overdoses and mental illness is an increasing problem in the community. Ambulance services are at the forefront of managing this challenging group of patients in the community who then require acute medical care. ABD can lead to patient and staff injuries as well as property damage if the ABD is not managed effectively and safely in a time critical manner. This area of ambulance work in Queensland is currently topical with an increasing number of assaults on Queensland Ambulance Service (QAS) staff.

In current practice, the QAS use midazolam both intravenously (IV) and occasionally intramuscularly (IM) for ABD. Haloperidol is also available but rarely used. Research over the last 10 years into ABD in the emergency department (ED) has shown that midazolam has an increase adverse effect profile in comparison to droperidol, a short acting typical antipsychotic^{1,2}. In addition there is an increased requirement for additional sedation in comparison to droperidol¹. When both drugs are used IM they appear to be equally effective in the time required to achieve sedation¹. When a standardised IM protocol for ABD is used, time to sedation is reduced, re-sedation rates are lower and the number of drug administrations is reduced³. Currently, the QAS preferentially use midazolam IV.

Droperidol has been used effectively and safely for migraine, as an antiemetic and for sedation by emergency physicians and anaesthetists for many years. In 2001 the federal drug administration (FDA) in the United States introduced a black box warning for droperidol for prolonged QT. Since this time, a number of studies on the use of droperidol for ABD in the ED setting have reported its safety from a cardiac perspective. In 2015 a large prospective observational study (>1000 patients) looking at the cardiac safety of droperidol also demonstrated a lack of QT prolongation with the doses commonly used for ABD⁴. This was accompanied by an editorial⁵, which was critical of the FDA's black box warning process on droperidol because there was of a lack of evidence in the peer reviewed scientific literature.

Droperidol has also been studied in the prehospital setting. A placebo randomised controlled study of 5mg IV droperidol versus saline demonstrated its effectiveness⁶ and a one year pilot study of IM droperidol in 53 patients also showed a similar effect⁷. A retrospective study assessed the safety of droperidol and midazolam (before and after ceasing droperidol use after the FDA warning) showed an increase incidence of adverse effects with midazolam in comparison to droperidol⁸.

Based on the research of ABD in the hospital and prehospital setting, the QAS plan to replace midazolam with droperidol for the drug management of ABD in the prehospital setting. An audit of this change of management of ABD will be undertaken by way of a prospective observational study.

Aims:

1. Assess the safety of droperidol and midazolam for ABD in the prehospital setting.
2. Assess the effectiveness of droperidol and midazolam for ABD in the prehospital setting.

Hypotheses:

1. IM droperidol will have a safer or lower adverse event rate than midazolam when used for ABD by QAS.
2. Time to sedation with the use of droperidol IM will be shorter than midazolam used IM and IV.
3. The requirement for additional sedation will be lower for droperidol than midazolam.
4. The number of drug administrations will be lower for droperidol than midazolam.
5. The use of IM droperidol will result in fewer injuries to patients and QAS staff.
6. Prehospital time will be shorter for patients receiving droperidol than midazolam.

Research Plan:

Study group:

Colin Page	Clinical Toxicologist and Emergency Physician
Lachlan Parker	Executive Manager – Clinical Policy Development, Clinical Quality & Patient Safety, QAS
Stephen Rashford	Medical Director, QAS
Emma Bosley	Director, Information Support, Research & Evaluation, Office of the Commissioner, QAS
Katherine Isoardi	Emergency Physician & Medical Officer, QAS
Fran Williamson	Emergency Physician & Medical Officer, QAS

Study Design & Setting:

This will be a prospective observational study, as part of a quality assurance monitoring process of replacing midazolam with droperidol for the management of ABD in the QAS. Although it is anticipated that the replacement of midazolam for droperidol will occur statewide across Queensland, the study will be undertaken in the Brisbane North and South Metro area.

Ethics and public health application (PHA) applications will be undertaken through Princess Alexandra Hospital & Queensland Health respectively. Site specific application is not required by QAS, but a similar administrative process is still undertaken. Since this is an observational study of clinical practice, patient consent is not required. The use of patient outcomes for research purposes without consent will be covered under the PHA application. The PHA is required for the release of confidential information for the purposes of research under the provision of Section 280 of the Public Health Act 2005.

Participants:**Inclusion criteria:**

1. Patients presenting with ABD ≥ 16 years of age with a sedation assessment tool⁹ (SAT) score ≥ 2 (below).

Exclusion criteria:

1. Patients presenting with ABD < 16 years of age.
2. Patients with known adverse effects e.g. dystonic reaction or known allergy to droperidol or midazolam.
3. Patients with Parkinson's disease.

Table 3. Sedation assessment tool (SAT)

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	Nil

Protocol:

A drug treatment protocol (DTP) for midazolam currently exists which covers ABD. It advises 2.5-5.0mg IV or 5mg IM which can be repeated every 5 (IV) – 10 (IM) minutes to a total dose of 25mg. Smaller doses are advised for patients >70 years. A DTP for droperidol has been developed for QAS. It recommends droperidol 10mg IM for patients aged 16 to 64 years and droperidol 5mg IM for patients \geq 65 years of age. This can be repeated after 15 minutes to a maximum dose of 20mg and 10mg respectively. Use of droperidol in \geq 65 years of age is undertaken only after consultation with a QAS medical officer. Consultation with a QAS medical officer can also occur if patients fail to sedate after 2 doses of droperidol.

Data Collection:

A purpose designed ABD audit form has been developed for QAS officers to use for all patients presenting with ABD where drug therapy is required. This will be completed and then photographed and emailed using the QAS supplied iPad to ABD.audit@ambulance.qld.gov.au. Review of the audit forms will occur in real time (<24 hours) and missing data, illegible recording etc. will be followed up by the research team. The audit form will not replace the standard recording performed by QAS officers' i.e. electronic Ambulance Report Form (eARF). This will also be reviewed for any missing data.

Study Outcomes:

The primary outcome will be the proportion of patients with adverse events comparing those given midazolam and those given droperidol. Adverse events are defined as:

1. Airway obstruction requiring an airway maneuver i.e. chin lift/jaw thrust through to LMA/Intubation.
2. Oxygen saturations < 90% on room air and/or respiratory rate < 12/minute
3. Systolic blood pressure <90mmHg.
4. A SAT score of -3
5. Dystonic reactions

Secondary outcomes:

1. Time to sedation defined as the QAS arrival time at patient until the SAT score decreases by 2 points or more or there is a score of zero.
2. The requirement for additional sedation, defined as any medication administered for the purpose of sedation within 60 minutes of achieving sedation defined in secondary outcome 1 above.

3. The number of drug administrations used to sedate patients with midazolam and droperidol.
4. Number of injuries to patients and QAS staff.
5. Prehospital time defined as QAS arrival time at patient to time of arrival at destination (receiving hospital).

Sample Size:

The sample size is based on the adverse event rates of midazolam and droperidol taken from previous studies.

Midazolam^{1,2}: 15 out of 91 patients – 16.5% (95% confidence interval Wilson's continuity correction 10.3% – 25.4%)

Droperidol^{1,4}: 71 out of 1433 patients – 5.0% (95% confidence interval Wilson's continuity correction 4.0%-6.3%)

Using these respective adverse event rates for midazolam (16.5%) and droperidol (5%), power of 80% and a statistical significance of 0.05, it is calculated that 260 cases of ABD (130 each group) is the sample size required for the study using Chi square analysis with continuity correction. An audit of ABD cases in the study areas for the six-month period July-December 2015 reported 142 cases. It is envisaged that the study will commence by the June 1st 2016 with the introduction of droperidol (depending on the administrative process) sometime in late 2016.

Statistical Analysis:

Data will be entered into an Excel™ spreadsheet. The primary and secondary outcomes will be reported using descriptive statistics including medians, interquartile ranges and ranges for continuous data; and proportions with 95% confidence intervals for dichotomous outcomes. Appropriate statistical tests will be used for comparison between the two study groups.

Study monitoring:

Monitoring the use of the ABD audit form will be done throughout the study period. As the use of midazolam by QAS is current standard practice, the chief investigator will regularly review any adverse events of droperidol. The research group and an external reviewer will review any increase in adverse reaction rates from droperidol if it occurs.

References:

1. Isbister GK, Calver LA, Page CB, Stokes B, Bryant JL, Downes MA. Randomized controlled trial of intramuscular droperidol versus midazolam for violence and acute behavioral disturbance: the DORM study. *Ann Emerg Med.* 2010 Oct;56(4):392-401
2. Spain D, Crilly J, Whyte I, Jenner L, Carr V, Baker A. Safety and effectiveness of high-dose midazolam for severe behavioural disturbance in an emergency department with suspected psychostimulant-affected patients. *Emerg Med Australia.* 2008 Apr;20(2):112-20.
3. Calver LA, Downes MA, Page CB, Bryant JL, Isbister GK. The impact of a standardised intramuscular sedation protocol for acute behavioural disturbance in the emergency department. *BMC Emerg Med.* 2010 Jun 28;10:14.
4. Calver L, Page CB, Downes MA, Chan B, Kinnear F, Wheatley L, Spain D, Isbister GK. The Safety and Effectiveness of Droperidol for Sedation of Acute Behavioral Disturbance in the Emergency Department. *Ann Emerg Med.* 2015 Sep;66(3):230-238.
5. Newman D. Training the Mind, and the Food and Drug Administration, on Droperidol. *Ann Emerg Med.* 2015 Sep;66(3):243-5.
6. Rosen CL, Ratliff AF, Wolfe RE, Branney SW, Roe EJ, Pons PT. The efficacy of intravenous droperidol in the prehospital setting. *J Emerg Med.* 1997 Jan-Feb;15(1):13-7.
7. Hick JL, Mahoney BD, Lappe M. Prehospital sedation with intramuscular droperidol: a one-year pilot. *Prehosp Emerg Care.* 2001 Oct-Dec;5(4):391-4.
8. Martel M, Miner J, Fringer R, Sufka K, Miamen A, Ho J, Clinton J, Biros M. Discontinuation of droperidol for the control of acutely agitated out-of-hospital patients. *Prehosp Emerg Care.* 2005 Jan-Mar;9(1):44-8.
9. Calver LA, Stokes B, Isbister GK. Sedation assessment tool to score acute behavioural disturbance in the emergency department. *Emerg Med Australia.* 2011 Dec;23(6):732-40.