

TITLE

Safety and Effectiveness of High Dose Midazolam for Severe Behavioural Disturbance in an Emergency Department with suspected psychostimulant-affected patients

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RUNNING TITLE

Psychostimulant management with Midazolam in the ED

AUTHOR CONTRIBUTIONS

DS contributed to study concept and design, acquisition of data, critical revision of manuscript, study supervision and administrative support; JC contributed to study design, acquisition of data, data analysis, drafting and submission of manuscript; VC LJ, AB and IW contributed to the study design, data interpretation and critical revision of manuscript.

COMPETING INTERESTS

This research was funded by the Australian Government Department of Health and Ageing. Outcomes of this pilot study assisted the development of emergency department and ambulance service national guidelines for the treatment of patients suffering acute psychostimulant intoxication.

Abstract

Objectives: To trial high dose midazolam sedation protocol for uncooperative patients with suspected psychostimulant-induced behavioural disorders. End-points were effectiveness and safety.

Methods: A prospective pilot study was undertaken with a convenience sample of adult, uncooperative patients with suspected psychostimulant-induced severe behavioural disorders. The protocol was Midazolam in 10mg increments, intramuscularly (IM) or intravenously (IV), at 10 minutely intervals, up to four doses and titrated to an end-point of rousable drowsiness.

Results: Sixty-two patients were enrolled. Two thirds of the patients required only one dose of Midazolam; 88% of the sample were sedated with two doses. Six and a half percent of patients were not sedated after four doses. A Glasgow Coma Score (GCS) of eight or less was prolonged in eight patients. Airway problems requiring an adjunct were present in four patients. Recent psychostimulant use was present in only 55% after full assessment.

Conclusions: High dose midazolam protocols cannot be supported as universally safe. High dose protocols for severe behavioural disturbance are not more effective with failures occurring even after repeated dosing.

Key Words: *emergency, midazolam, psychostimulants*

Introduction

Psychostimulants have been identified as a major drug of concern in Australia¹ and the growing prevalence of use has been recognised nationally² and internationally.^{3,4} More than one in five 20-29 year old Australians have reportedly used amphetamine or ecstasy.⁵ This prevalence within society has been accompanied by an increase in presentations to treatment services⁶ such as emergency departments (ED)s³, ambulance⁷ and police services.⁸

In the acute stage, patients under the influence of psychostimulants may present with more energy, alertness and excitation.⁹ Long-term or regular use of amphetamines may lead to significant health problems such as anxiety, high blood pressure, amphetamine psychosis (which includes hallucinations, paranoia and other symptoms similar to schizophrenia), reduced immunity, and risk of damage to brain cells.^{10,11} These effects can make assessment and management difficult.¹²

ED staff frequently provide care for patients who are sometimes violent as a result of suffering from drug or alcohol intoxication and/or mental disorder.^{13,14} Chemical restraint is sometimes required for these patients in order to protect their safety and that of others. In Australasian EDs, commonly used and available chemical restraints include haloperidol, droperidol, midazolam and diazepam^{13,15} but often these are believed to be administered in insufficient doses.¹⁶

This study occurred at a time when a perception existed that an epidemic of psychostimulant use was to blame for increasingly frequent episodes of violence in the community. Whether this perception was correct and if these patients could be specifically identified was questioned. Previous research regarding the administration of midazolam as a sedating agent for severe behavioural disturbance has not specifically identified what proportion are psychostimulant users. Behaviourally disturbed patients are frequently attended to by ambulance and police officers who then need to bring them to a hospital ED. There is a need for protocols for sedation that could be used in the prehospital setting to make this transport safer for the patients and prehospital staff. As safety is of paramount importance it was decided to evaluate a sedation protocol used for patients under the suspected influence of psychostimulants within an emergency setting that encompassed safety and effectiveness issues.²

Midazolam is the only benzodiazepine licensed for paramedic use throughout Australia. There is limited research into the effectiveness and safety of utilising midazolam as a sedating agent for patients presenting to the ED in an acutely behaviourally disturbed state as a result of psychostimulants. It has been a clinical observation that high doses of sedating agents are frequently needed for this patient group. Thus, the hypotheses guiding the study on this patient population were:

1. Midazolam, administered in higher doses, is likely to be effective;
2. Midazolam, administered in higher doses, is likely to be safe.

Methods

Study Setting, Sample, Design. The setting for this study was the ED of the Gold Coast Hospital (GCH). The GCH ED is a metropolitan hospital that has approximately 62,000 patient presentations annually. Sixty-two adult patients with severe behavioural disturbance suspected to be from psychostimulant use were prospectively enrolled by protocol informed ED consultants or registrars in this observational pilot study. All ED staff were involved in selection of patients for study inclusion. The study ran from August 2003 - December 2005. Criteria for suspicion of psychostimulant use were: suspected drug induced psychotic symptoms, physical appearances consistent with regular psychostimulant use, extremely agitated or aggressive behaviour, patient was a known drug user, self report, collateral report from accompanying persons, police or ambulance officers. Inclusion criteria for study enrolment were: patients whose behavioural disturbance was an immediate danger to self or others and suspicion of psychostimulant use. Exclusion criteria were: use of other sedation drugs during protocol, aged under 16 years, known allergy to midazolam, temperature ≥ 38 degrees Celsius (due to possibility of other underlying medical illness or hyperthermia), cooperative with oral sedation or verbal and behavioural de-escalation measures, suspected organic cause requiring urgent investigation or treatment.

A high dose parenteral midazolam protocol was to be tested for effectiveness and safety. The protocol was Midazolam in 10mg increments, intramuscularly (IM) or intravenously (IV), at 10 minutely intervals, up to four doses and titrated to an end-point of rousable drowsiness. The choice of route was not controlled due to known clinician variation in preference, typically based on individual patient factors and immediate safety considerations.

Effective sedation was defined as the patient being asleep or awake and cooperative. Rousable drowsiness was defined and considered ideal and safe sedation when GCS equalled 9-15 in combination with patient cooperation and compliance. Requirement for subsequent rescue medication was defined as the need to give further sedation within 60 minutes of the last apparently effective protocolised dose. Safety was to be evaluated by examination of defined failed safety criteria occurring during the protocol time or within four hours following the administration of the last dose of midazolam. Failed safety criteria were identified as: need for airway adjunct, hypotension (BP < 90mmHg), respiration rate < 12 breaths per minute, SaO₂ ≤ 90%, Glasgow Coma Scale (GCS) eight or less, unplanned intensive care admission or significant aspiration event. Tachycardia is a frequent indicator of psychostimulant toxicity¹⁷ and was thus not considered a marker of instability.

The protocol for routine care of a sedated patient included supplemental oxygen, recovery position, vital sign monitoring and de-identified urine drug

analysis. Education sessions detailing enrolment, protocol requirements and study updates were provided to ED medical officers, ED nurses, security and the emergency psychiatric services staff. Staff were made aware that patient safety was of primary importance and if a critical event for any of the enrolled patients occurred, the study was to be terminated. Two study members (DS and JC) worked regularly within the ED. Thus, they were able to track the enrolment process. DS monitored each enrolment for critical events within 24 hours of enrolment during the trial. Data analysis was performed by JC. Any uncertainties in the review process were resolved with a separate review (by DS and JC). Missing data arising from inconsistencies with the recording of vital observations affected the level of data analysis able to be performed. For example, as not every patient had a GCS recorded at stipulated intervals, analysis was limited to whether GCS was recorded as ≤ 8 within 4 hours post midazolam administration. The power of the study allowed immediate trial cessation to occur if a single critical event occurred. Critical events defined in advance included death, intubation, unplanned intensive care admission, a significant aspiration event or other unanticipated major adverse outcome. ED staff were not blinded to these. The study was approved by the Gold Coast Health Service District Ethics Committee (RAN: 200332).

Data Analysis. Frequencies (percentages) were used to report categorical data and, depending on distribution, continuous data were reported as mean and standard deviation (SD), or median and interquartile range (IQR). A power

calculation revealed that a total of at least 60 patients would allow for the detection of 95% of critical events with an incidence of 5%. An upper confidence interval $\leq 2\%$ was set if nil critical events were to be detected among the 60 patients. Data were analysed using the Statistical Package for Social Sciences (SPSS Inc. Chicago, Ill, USA) version 12.

Results

A total of 62 patients were enrolled in the trial. The demographics of the sample along with characteristics of their ED presentation can be viewed in Table 1.

(INSERT TABLE 1 ABOUT HERE)

Clinicians were not easily or specifically able to identify the study's targeted psychostimulant population on entry to the study. Most of the patients had a past or current drug or alcohol abuse history (Table 1). Current drug use related to the attendance was confirmed in 48 cases, 2 further were suspected drug induced with a collateral past history of frequent drug related presentations. Examination of current drug use history revealed that polysubstance abuse and frequent concomitant alcohol abuse was the commonest pattern of drug abuse. Psychostimulant use was identified in just over half of all patients, but only two of those used psychostimulants alone. Some patients had massive ingestions of

sedative agents including benzodiazepines, physopentone and alcohol immediately prior to arrival.

Urine drug screens were requested on all patients but only obtained from 34 (55%, 95% CI 42-67). Of the 34 samples tested, 29 (85%, 95% CI 68-95) detected an illicit substance. Spectrophotometric analysis was also obtained from 28 of the 29 positive urine drug screens. Of those 28, 9 (32%, 95% CI 17-52) were positive for psychostimulants (Metamphetamine, amphetamine sulphate, MDMA, cocaine), 23 for cannabinoids, 5 opiates. Many had more than one substance detected. A blood alcohol level (BAL) was not protocolised but 38 patients had BAL and 11 (29%, 95% CI 16-46) were positive with levels all suggesting significant intoxication (Range 0.1% - 0.7%).

Effectiveness

The four dose regime midazolam protocol was effective for 94% of the sample. However, the majority were effectively sedated with one or two doses: sixty seven percent with a single dose and a further 21% with a second dose (Table 2). IM was the most common route of administration for the first dose of midazolam, while IV was more common for second and subsequent doses.

(INSERT Table 2 ABOUT HERE)

Midazolam was initially the only drug prescribed but after apparent success additional rescue medications such as haloperidol, diazepam or olanzapine were administered to 13 (21%, 95% CI 12– 34) patients during their ED stay (Table 3).

(INSERT Table 3 ABOUT HERE)

Safety

The midazolam sedation protocol was deemed safe if no failed safety criteria occurred. Table 4 shows the 19 occurrences of failed safety criteria where low blood pressure (< 90 mmHg), low GCS (≤ 8), low respiration rate (<12 breaths per minute), oxygen saturation <90% and airway adjuncts were recorded based on the number of doses of midazolam administered. In total, 15 patients (24%, 95% CI 15-37) failed one or more safety criteria. The accumulated number of failed safety criteria increased with dose as follows: 9 noted after one dose, 17 after two doses, 19 after three doses. No further increase occurred in a small patient group after four doses. None of the 62 patients were intubated, but four patients required an airway adjunct (3 nasopharyngeal, 1 oropharyngeal). These four received only one or two doses of midazolam. Additionally, of nine patients with a GCS of eight or less, eight had a prolonged (more than 30 minutes) decrease in GCS. One of these patients with prolonged reduction in GCS and use of an airway adjunct was identified to have taken a massive intravenous dose of pharyseptone prior to arrival. Hypotension was noted in seven

patients and none were found to have a recorded respiratory rate <12 or SaO₂ of $\leq 90\%$. There were no clinically evident aspiration events and no intensive care admissions.

(INSERT TABLE 4 ABOUT HERE)

The number of failed safety criterion that occurred with each dose was examined based on route of administration (Table 5). The proportion of failed safety criterion that occurred following the first dose of midazolam was lower in the IM alone group (7%) compared to the IV alone group (14%). Following a second dose of midazolam, there were no further failed safety criterion after IM midazolam but there were further failed safety criteria after IV alone (25%) and the IM followed by IV group (33%).

(INSERT Table 5 ABOUT HERE)

Discussion

The patient population studied was selected as likely representing an epidemic of psychostimulant abuse with subsequent severe behavioural disturbance. Patient history suggested that just over half used psychostimulants proximate to this attendance. The specific urine chromatography data, when obtained, indicated only 32% were under the influence of such. This lower

incidence on drug screening may reflect reluctance to provide urine samples in illicit drug users. Additionally, previous studies have often shown negative urine screens in known amphetamine users with psychosis likely due to drug cessation many hours to days or even weeks before ED presentation.^{18,19} Illicit polysubstance abuse however was the most commonly evident drug use pattern. This and the male predominance in the population is typical.^{6,17} The study was not designed to capture specific alcohol intoxication but historical information and non-protocolised testing by clinicians showed a high frequency of alcohol intoxication. This alcohol use occurred either alone or more commonly in association with polysubstance abuse. Overall, at least 85% of presentations could be linked to intoxication with alcohol or illicit drugs. There was a low frequency of psychiatric illness in the absence of intoxication consistent with the study design. Therefore objective analysis indicates that clinicians were poor at distinguishing the precise aetiology of severe behavioural disturbance without detailed history, examination and special investigations. The study affirms the perception that psychostimulants are a major contributor, but not the exclusive reason for episodes of violence and severe behavioural disturbance in our community.

Most of this patient group (82%) were considered disturbed enough to require transport to hospital by police or ambulance and treatment in an ED. They are labour and resource intensive during physical restraint and transport. Injuries to patients and staff can occur during physical restraint²⁰ and the

occurrence of sudden patient death has been reported.^{12,21} There is significant safety risk to staff and patients while the severe behaviour continues and is uncontrolled. The high incidence of involvement of police and ambulance personnel justifies research for safe and effective protocols that can be used to control behaviour in the prehospital environment.

Effectiveness

Previous studies have considered midazolam as an effective sedative agent for violent and severely agitated patients and for patients with a mental disorder.^{15,16,22,23} Studies using doses from 5-15mg IM or IV have shown effectiveness in the range of 55% at 10 minutes in IV groups, increasing to 83-89% at twenty minutes for IV or IM, and 77-90% for IV or IM at 30 minutes. IV therapy has been shown to be more rapid in onset but with increased risk of airway intervention.¹⁵ The present findings indicate this protocol is similarly effective, sedating 68% at 10 minutes, 89% by 20 minutes and 92% by 30 minutes. However this twenty and thirty minute response has required two or three doses to get similar results obtained from a single dose of 5-15mg IM used in previous studies.^{16,22} The high dose protocol with frequent dosing has thus not achieved obvious or dramatic improved sedative effect compared with normal dose or other high dose protocols.^{15,16,22,23} In fact, the majority of patients were sedated after 2 doses, if they were eventually sedated (55/58, 95%). The lack of improved effectiveness from further doses likely reflects a group of tolerant patients have been selected by non response to first or second dosing.

Safety

Previous studies that reported midazolam as a safe sedation agent for patients in the ED are now over 15 years old and focussed on the sedation of psychiatric patients. They were not directed to drug related presentations.²⁴⁻²⁶ More recent studies have reported variable safety concerns when used on groups containing significant numbers of both patient groups.^{15,16,22,23} Risk of interaction with unknown drugs and alcohol are a known concern when sedating an intoxicated individual. Leichti et al.¹⁷ reported a GCS of less than 8 in 17 (33%) ecstasy-intoxicated patients in their study but only 13 (25%) of the patients in the overall study group were given benzodiazepines. It is difficult to compare their findings with ours as it is unknown what proportion of their patients who had a GCS of less than eight also received sedation. Nevertheless, it indicates that even without the administration of sedation, the GCS of a patient who is reportedly under the influence of psychostimulants (such as ecstasy) can vary, possibly as a result of other drugs or alcohol.¹⁷ One of our patients with failed safety criteria had massive physeptone dosing immediately prior to arrival. Others had taken massive amounts of benzodiazepines or alcohol but did not have failed safety criteria. This highlights known difficulties during sedation of this diverse patient population.

There were no identified critical effects however there were failed safety criteria 19 patients. Hypotension in some patients was typically brief and observed outcome benign regardless of intravenous fluid usage. No patients had a respiratory rate of less than 12. Lack of any demonstrated hypoxia is in contrast to previous reported studies^{15,23} and likely relates to our protocol requiring supplemental oxygen after sedation. Some patients did however, require airway adjuncts to maintain an airway, indicating some significant risk and need for skilled clinician intervention.

A GCS of eight or less exceeded 30 minutes in eight (13%) of the 62 patients on repeated observations. This suggests a genuine reduction of GCS was present. The study protocol advised patients should be placed on oxygen in the recovery position post sedation. This instruction may have biased clinicians against more active airway management. The clinician belief that midazolam typically has a short sedation duration may additionally have created a false expectation that patient's GCS was likely to rapidly improve. The alternative to use Flumazenil to reverse sedation is not local practice and considered high risk by most clinicians.²⁷⁻³⁰ A strong argument could be made that these patients had an unprotected airway²⁷ and that intubation was indicated. If intubation was performed, up to eight critical events would have occurred from 62 patients. That such prolonged sedation occurred in eight separate cases without any immediate physician or nurse awareness we believe is highlighted for clinicians and potential future research.

Adverse effects have been reported in other studies where midazolam was used for sedating violent patients.^{15,22} Huf et al.²² reported one adverse event when 15 mg of midazolam IM was administered to a man with alcohol induced, and perhaps also cocaine induced, aggression. His respiratory rate fell and he became cyanotic, requiring IV Flumazenil to recover. Nobay et al.¹⁶ had no reported adverse effects with midazolam 5mg IM, but reported two with haloperidol (one hypotension, one apnoea). Martel et al. reported respiratory depression requiring oxygen in 10 of 48 patients with midazolam 5mg IM.²³ Knott et al.¹⁵ (with a more frequent midazolam 5mg dose intravenous protocol), also demonstrated airway problems and hypoxia. They reported clinician intervention was needed for four of 74 patients, representing indicators that the high dose midazolam protocols are potentially unsafe.¹⁵ The potential requirement for airway intervention mandates the need for rapid access to persons with advanced airway management skills when these drugs are used.

Airway adjunct requirement and prolonged low GCS were noteworthy failed safety criteria that most commonly occurred with the first and second dose of midazolam. The reported incidence of failed safety criteria appears increased when compared to previous IM studies using a normal therapeutic dose of 5mg midazolam.^{16,23} These observations indicate that many patients do not have above normal tolerance to midazolam as hypothesised in the study design. Safety of the high dose midazolam protocol has not been proven.

Limitations

Whilst the study was conducted prospectively, data was recorded by the treating clinician (nurse or doctor) which did not guarantee accurate and complete information despite repeated education sessions and well placed information sheets. As such, missing data limited the level of analysis able to be performed. The small sample size and the study being conducted in a single ED, means that external validity may be a limiting factor. This was only an observational study and the lack of randomisation, controls and comparison between IV and IM or doses of midazolam makes it not possible to make any definitive clinical conclusions about the effectiveness of midazolam.

Conclusion

The high dose midazolam sedation protocol utilised for this study was most effective with the first and the second dose, but was not universally effective. Significant safety concerns are evident with potential therapeutic overdose occurring with the high dose regimen. These were most common with the first and second doses. The use of a modified protocol within the ED and prehospital setting utilising a therapeutic first dose of midazolam intramuscularly and allowing sufficient time for action may be safer, however further research is needed.

Acknowledgements

The authors wish to thank the continued involvement from the Gold Coast Hospital Emergency Department and pathology staff in this research project.

This pilot study was supported by funding from the Australian Government Department of Health and Ageing.

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Table 1. Characteristics of Sample

Characteristics	Total N = 62	Frequency (%)
Mean age in years (\pm SD)	27.8	\pm 8.4
Gender		
Male	35	57%
Female	27	44%
Mode of Transport to Hospital		
Ambulance	26	42%
Police	25	40%
Private Vehicle	11	18%
Median ED LOS (IQR) hours	10	5-14
†History		
Prior Drug or alcohol abuse	51	82%
Prior Mental health	37	60%
Prior Medical Condition	16	26%
†Current Drug Use history		
Psychostimulants	34	55%
Cannabis	28	45%
Alcohol	27	44%
Benzodiazepines	11	18%
Opiates	7	11%
Gamma Hydroxy Butyrate	2	3%
LSD	1	2%
Polydrug abuse pattern	37	60%
Final Diagnosis		
Drug Induced Psychosis	25	40%
Drug Induced Psychosis (Suspected)	2	3%
Psychosis – No drugs suspected	4	7%
Agitation or aggression – drug related	9	15%
Agitation or Aggression – drug and alcohol related	15	24%
Agitation or Aggression – alcohol related	4	7%
Agitation or Aggression – No drugs or alcohol or medical cause	1	2%
Agitation or aggression – Medical cause likely. No drugs or alcohol	2	3%
Total With Drug or Alcohol Related Final Diagnosis	54	87%

SD=Standard deviation; IQR=Inter-quartile range, LOS=length of stay; ED LOS includes time spent in observation ward; † Some patients had more than one history

Table 2. Effectiveness by route and dose of Midazolam.

Dose	Route of administration			Total (all routes)	Cumulative Total (all routes)
	IM Alone	IM First Dose + IV	IV Alone		
Dose 1	30/41 (73%)	- ¹	12/21 (57%)	42/62 (68%)	42/62 (68%)
Dose 2	2/3 (67%)	6/9 (67%)	5/8 (63%)	13/20 (65%)	55/62 (89%)
Dose 3	n/a	1/3 (33%)	1/4 (25%)	2/7 (29%)	57/62 (92%)
Dose 4	n/a	0/2 (0%)	1/3 (33%)	1/5 (20%)	58/62 (94%)

NB. Numbers and percentages are presented as occurrences within each group;

¹ See IM alone.

Table 3. Rescue Incidence by Route and Dose of Midazolam

Dose	Route of administration			Total (all routes)	Cumulative Total (all routes)
	IM Alone	IM First Dose + IV	IV Alone		
Dose 1	2/41 (5%)	⁻¹ See IM alone	3/21 (14%)	5/62 (8%)	5/62 (8%)
Dose 2	0/3 (0%)	2/9 (22%)	1/8 (13%)	3/20 (15%)	8/62 (13%)
Dose 3	n/a	0/3 (0%)	1/4 (25%)	1/7 (14%)	9/62 (15%)
Dose 4	n/a	2/2 (100%)	2/3 (67%)	4/5 (80%)	13/62 (21%)

NB. Numbers and percentages are presented as occurrences within each group

¹ See IM alone.

Table 4. Failed Safety Criterion by Dose

Dose	Failed Safety Criterion			Number patients with failed safety criterion	Cumulative Total (failed safety criteria)
	GCS (≤ 8)	Airway adjunct	BP (< 90 mmHg)		
Dose 1 (n=62)	4 (7%)	2 (3%)	3 (5%)	7 (11%)	9/62 (14%)
Dose 2 (n=20)	3 (15%)	2 (10%)	3 (15%)	7 (35%)	17/62 (27%)
Dose 3 (n=7)	1 (14%)	0 (0%)	1 (14%)	1 (14%)	19/62 (31%)
Dose 4 (n=5)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	19/62 (31%)

NB. Numbers and percentages are presented as proportion of dosage group

Table 5. Incidence of Failed Safety Criterion by dose and route of administration

Dose	Route of administration			Total (all routes)	Cumulative Total (all routes)
	IM Alone	IM First Dose + IV	IV Alone		
Dose 1	3/41 (7.3%)	- ¹	3/21 (14.3%)	6/62 (9.7%)	6/62 (9.7%)
Dose 2	0/2 (0.0%)	3/9 (33.3%)	2/8 (25.0%)	5/20 (25.0%)	11/62 (17.7%)
Dose 3	n/a	1/3 (33.3%)	0/4 (0.0%)	1/7 (14.3%)	12/62 (19.4%)
Dose 4	n/a	0/2 (0.0%)	0/3 (0.0%)	0/5 (0.0%)	12/62 (19.4%)

NB. Numbers and percentages are presented as occurrences within each group;

¹ See IM alone.

