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Management of Behavioural Emergencies: A Prospective Observational Study in Australian Emergency Departments

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CY, DK, DT, ST and JK conceived and participated in designing the study. CY and DT undertook the data analysis. All authors contributed to data collection, interpretation of the

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Management of Behavioural Emergencies: A Prospective Observational Study in Australian Emergency Departments

Abstract

Aim

To describe the prescribing patterns and adverse events (AEs) associated with parenteral sedation for the management of behavioural emergencies (BEs) in Australian emergency departments (EDs).

Methods

Ten Australian EDs enrolled a convenience sample of adult patients (aged 18 years or more) requiring parenteral sedative medication for BEs. Data were collected prospectively between March 2015 and April 2017 using a designated case report form.

Results

A total of 564 cases were enrolled. Incomplete cases (17 cases, 3%) were excluded. Of the 547 remaining cases, 63% were male and the median age was 34 years (range 18 to 95 years). Approximately one half (230, 42.1%) of patients required mechanical restraint and parenteral sedation to manage their BEs. Intramuscular monotherapy was administered in most cases (390, 71.3%). The main sedative medications used as monotherapy were droperidol (381, 69.7%), midazolam (54, 9.9%) and olanzapine (26, 4.8%,). The most common combination therapy was midazolam + droperidol (36, 6.6%). The AE incidence from sedative administration was 13.5%. No death or irreversible AEs were reported.

Conclusions

Overall, the participating EDs provided safe pharmacological management for BEs. Adverse events following parenteral sedation are common although serious AEs are rare. As all patients receiving

parenteral sedation for BEs are at risk for AEs, ongoing monitoring of vital signs after parenteral sedation should be a standard protocol in all EDs.

Keywords

Behavioural emergencies, agitation, sedatives, parenteral sedation, adverse events, emergency department, prescribing patterns, monotherapy, combination therapy, antipsychotics, benzodiazepines.

Introduction

Patients with behavioural emergencies (BEs) commonly present to emergency departments (EDs), with staff frequently exposed to violent and aggressive behaviours. Australian studies have revealed that the majority of clinical staff working in the ED experience some form of violence at least weekly,[1] and in a recent study, an increasing trend in the incidence of violence was reported.[2] Behavioural emergencies are challenging to manage due to the need to make quick treatment decisions for patients unable to provide an accurate clinical history at presentation.

Current guidelines recommend managing BEs initially with oral sedative medications whenever possible.[3,4] This recommendation is based on expert opinion and consumer surveys which indicate that oral medication administration is less coercive and is perceived as less traumatic by psychiatric patients. However, there is a subset of agitated patients for whom parenteral sedation is the only feasible option. In a study by Hatta et al. [5] more than one half of eligible patients (118/208, 57%) refused oral medications and required management with parenteral sedation. Consequently, parenteral sedation has an important role in the management of BEs in EDs, especially for patients with severe agitation or patients who refuse oral medications.

Parenteral sedation for the management of BEs in the ED has typically involved the use of benzodiazepines, and antipsychotics.[4,6] Whilst monotherapies have been commonly used, several studies have shown that combination therapies provide significantly more rapid and effective sedation.[7-9] Other parenteral sedative medications such as ketamine have also been investigated for severely agitated patients in the ED.[10] It is unknown whether the publication of new evidence has translated into changes in prescribing patterns.

Patients presenting with BEs can be highly complex with co-morbid medical and substance abuse issues. Randomised controlled trials (RCTs) that investigated the safety and efficacy of parenteral sedation for BEs management suggest that adverse events (AEs) are common.[11] However, due to safety and ethical reasons, certain patient groups (e.g. patients aged above 65 years) are commonly excluded from RCTs. Given the limitations of RCTs, data on AEs from observational studies can complement RCT data.

The aim of this paper is to describe the prescribing patterns and AEs associated with parenteral sedation for the management of BEs in Australian EDs.

Method

Study Design and Study Population

This was a multi-centre prospective observational study undertaken in the EDs of ten Australian public, tertiary-referral hospitals across three states (i.e. Victoria [VIC], Queensland [QLD] and New South Wales [NSW) in Australia from March 2015 to April 2017. The annual patient census of these EDs ranged from 50,000 to 100,000 patients. Each ED is supported by 24-hour co-located psychiatric services. Ethical Committee approvals and site-specific authorisations were obtained from all the study sites. Due to the level of agitation during a BE, informed consent was not possible and waiver of consent was granted.

A convenience sample of patients aged 18 years or older and who required parenteral sedation for BE was enrolled at the participating EDs. There were no exclusion criteria. All participants were managed according to usual clinical practice and local hospital guidelines. The choice of parenteral sedation was entirely at the discretion of the treating doctor and was not stipulated by recruitment into the study. After sedation had been achieved, regular observations including pulse, respiratory rate, airway patency, skin colour, blood pressure and oxygen saturation were undertaken at least every 10-15 minutes for one hour.

Data Collection

Data were collected using a designated case report form. The occurrence of respiratory AEs (i.e. hypoventilation [respiratory rate < 10 breaths/min], oxygen desaturation [oxygen saturation <90% mmHg], partial or complete airway obstruction); cardiovascular AEs (i.e. prolonged QTc [corrected

QT > 500ms], tachycardia [heart rate > 100 beats per minute], bradycardia [heart rate < 60 beats per minute); and other AEs (i.e. extrapyramidal side effects [EPSE], vomiting, anticholinergic side effects [e.g. urinary retention, dry mouth], fall and anaphylaxis) were recorded by the ED staff as soon as they occurred. Outcome of the reported AE was reported as not resolved, resolved or resolved with sequelae. A serious AE was defined as death, life-threatening (e.g. respiratory arrest), or requiring hospitalisation (i.e. admission to medical wards or intensive care units due to the AE), or if deemed to have caused persistent disability.

Patient demographic, baseline characteristics data and information on parenteral sedation prescribed in the ED including name, dose, route and time of administration were collected retrospectively from the medical records by site investigators. For this study, combination therapy was defined as two different types of sedative medications administered within 15 minutes of each other.

Data Analysis

Two clinical trials investigating the management of BE in EDs reported that AEs occurred in 11.6%[9] and 13.7%[12] of patients. Our sample size was initially calculated to be at least 1944 patients in order to be 95% certain that the AE rate would range between 11% and 14% (level of significance 0.05). An interim analysis was conducted at the two-year point of the study, and because of the AE rate had reached 13.5%, (within the estimated range), the study was concluded.

Patient demographics, prescribing patterns, nature and frequency of AEs were analysed descriptively and reported as frequencies and percentages. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Medians are reported with ranges or interquartile ranges (IQRs) for continuous variables. Subgroup analysis for patients aged above 65 years was performed to examine parenteral sedation practice of elderly patients with BEs in the ED. All analyses were performed using IBM SPSS Statistics Version 24 (Armonk. NY: IBM Corp.). The level of significance was 0.05.

Results

Description of the presentations

The study was concluded at the two-year point with 564 cases enrolled. Seventeen cases were excluded due to incomplete information. Of the remaining 547 cases, there were 27 (4.9%) cases

from two EDs in NSW, 222 (40.6%) cases from five EDs in VIC, and 298 (54.5%) cases from three EDs in QLD.

Patient characteristics

A summary of the patient characteristics by initial choice of sedation regimens is reported in **Table 1**. Overall, there was a high prevalence of either alcohol or illicit drugs usage (or both). Among the 236 patients identified as ingesting alcohol prior to ED presentation, 19.5% (46/236, [95%) had blood alcohol concentrations documented. The mean (SD) blood alcohol concentration among these patients was 0.198 (0.1) g/dL. Of the 247 patients who admitted to using illicit drugs before the presentation, almost one half (106/247, [42.9%) reported methamphetamine use. Other illicit drugs that were used by these patients including cannabis (38/247, [15.4%, ecstasy (11/247, [4.5%), and gamma hydroxybutyrate (6/247, [2.4%). Polysubstance misuse was common; 113 (20.7%) patients had used both alcohol and illicit drugs, and 47 (8.6%) patients had used more than one type of illicit drug prior to the presentation.

Patients who received monotherapy or combination parenteral sedation therapy were of similar age and gender. However, more patients in the combination group had a final diagnosis of substance intoxication. Significantly more patients in the combination group were affected by illicit drugs (**Table 1**). Although the need for mechanical restraint was greater among patients in the combination group, the difference between those receiving monotherapy and combination parenteral sedation therapy was not statistically significant.

Initial choice of parenteral sedation

The initial choice of parenteral sedation, by route of administration, is described in **Table 2**. Overall, monotherapy was more commonly administered than combination therapy. The intramuscular (IM) route was preferred over intravenous (IV) route. However, NSW reported a significantly higher number of cases (33.3%) using IV route to administer monotherapy than VIC (8.0%) and QLD (22.4%).

Overall, the main sedative medications used as monotherapy were droperidol, midazolam and olanzapine. No significant difference was observed in the proportion of patients sedated with droperidol monotherapy among the three states ($p>0.05$). However, significantly more patients in

VIC (11.7% vs 1.5% in QLD and 0% in NSW) were sedated with olanzapine monotherapy (p <0.001); and significantly more patients in NSW (33.3% vs 5.3% in VIC and 14.7% in QLD) were sedated with midazolam monotherapy (p<0.001).

Droperidol, alone or in combination, was used in more than two-thirds of all cases (381/547; 69.7%), with IM droperidol 10mg being the most frequently prescribed regimen (293/547; 53.6%). When combination therapy was administered, droperidol was combined with midazolam more frequently than with other sedative medications. No significant differences were observed in the choice of combination therapy between the states, except the combination of droperidol and olanzapine, where all eight cases were reported by the participating EDs in VIC.

Adverse events

A total of 82 AEs was identified among 74 patients. The incidence of AE at the two-year point was 13.5% (74/547), within the estimated range. **Table 3** describes the frequency and nature of AEs. Respiratory AEs included oxygen desaturation, airway obstruction and hypoventilation were the most commonly reported AEs. All respiratory AEs were managed with the administration of oxygen, airway positioning, or bag-mask ventilation. No patient in this study required endotracheal intubation secondary to parenteral sedation, and no reversal drugs (e.g. flumazenil) were administered. One patient experienced anaphylaxis (attributed to droperidol) which resolved after a single dose of IM adrenaline. All other reported AEs were transient and resolved without adverse clinical outcomes. No deaths or other serious AEs were reported.

Subgroup analysis for patients aged above 65 years

There were 31 patients aged above 65 years and the median age of this subgroup was 81 years (IQR 75-87 years). The majority of this subgroup of patients were male (23/31; 74.2%). Among these, the main comorbidities associated with the BEs were dementia (11/31; 35.5%), alcohol intoxication (3/31; 9.7%), and urosepsis (2/31; 6.5%). Monotherapy was administered in nearly all cases (**Table 4**). The main sedative medications used as monotherapy in this subgroup of patients were droperidol, olanzapine, midazolam and haloperidol.

AEs were documented over a quarter of the > 65 year old cases (8/31; 25.8%). Reported AEs were oxygen desaturation (3/31; 9.7%), bradycardia (2/31; 6.5%), anticholinergic side effects (i.e. dry

mouth, difficulty urinating) (2/31; 6.5%), QTc prolongation (1/31; 3.2%), and tachycardia (1/31; 3.2%). All AEs reported in this subgroup of patients were resolved without adverse clinical outcomes.

Discussion

To our knowledge, this is the largest prospective observational study of BE management in Australian EDs and it has provided pivotal insight into current clinical practice. Our study demonstrates that droperidol is the most common monotherapy prescribed for the management of acute agitation in Australia. This differs from other countries, where haloperidol is the first choice for sedation of acutely agitated patients in the United States of America (USA),[6] the United Kingdom,[13] Europe[14] and Hong Kong.[15] This difference might relate to the limited availability of droperidol in these countries. In 2001, a black-box warning was issued for droperidol by the USA Food and Drug Administration because of a risk of development of torsade de pointes induced by QT prolongation.[16]

Our findings demonstrate a noticeable change in the prescribing pattern for the management of BE in the Australian setting. In a survey conducted in 2009, midazolam was reported as the most preferred choice of parenteral sedation for agitation management among Australasian College of Emergency Medicine members,[17] and it is the first-line therapy recommended in the Therapeutic Guidelines for behavioural emergencies.[4] The increasing number of studies documenting efficacy and safety of droperidol in the Australian ED setting in the last five years,[9, 18, 19] may have reduced markedly the preference for midazolam. Furthermore, the publication of state health policies from both NSW[20] and QLD[21] in 2015 may also have contributed to the observed changes in the prescribing pattern. In our study, droperidol 10mg was the most commonly prescribed dose, which is consistent with the dose used in several clinical studies.[7, 12, 19, 22] Whilst emerging data from observational studies show that ketamine appears to be effective in managing severely agitated patients,[10] it was not commonly used in the participating EDs.

The cause of BEs is often multifactorial. Patients may present with (i) acute psychosis (e.g. first episode of psychosis or with underlying mental illness) with no detectable underlying medical disease; (ii) dual diagnosis (i.e. individuals with both psychiatric and substance use disorders); (iii) acute psychosocial crises (e.g. suicidal, deliberate self-harm); (iv) substance intoxication or withdrawal (e.g. simple alcohol intoxication, methamphetamine overdose.); or (v) organic disorders

without underlying psychiatric disorders (e.g. hypoglycaemia, hyperthyroidism).[4] Our study shows that more patients with a final diagnosis of substance intoxication required parenteral sedation for BEs than those with a final diagnosis of mental illness. This suggests that patients intoxicated with either alcohol and/or illicit substances may not respond adequately to non-pharmacological interventions (e.g. verbal de-escalation) and may not accept oral medications. Further studies investigating the efficacy and safety of various parenteral sedation regimens for the management of illicit substances-related agitation in the ED are required to ensure optimal management of this subgroup of patients.

Although most of our patients were managed with monotherapy, it is notable that a wide variety of sedative combinations are used, albeit in small numbers. Whilst there is high-quality evidence that supports the efficacy advantage of adding a benzodiazepine to an antipsychotic,[8] the use of two antipsychotics e.g. droperidol and olanzapine has not been well studied. As droperidol and olanzapine both have anticholinergic effects and increase the risk of seizures, the concurrent use of these two antipsychotics may increase the risk of AEs, which include central anticholinergic delirium.[23] Hence, these combinations should be used with caution. The practice of 'experimentation' with different sedative medications highlights the need to develop and to promote the use of a standardised guideline for the management BEs in VIC. We did not specifically collect data on the rationale for combination parenteral sedation therapy and as such cannot comment on the individual clinicians' choice.

Our findings that respiratory AEs were the most common AEs are consistent with previous RCTs of different sedative medications in the management of acute agitation.[7, 9, 12 ,22] Given the transient nature of most respiratory AEs, it is possible that some of the respiratory events were not recorded. The frequency of these AEs, and their transient nature, highlight the need for meticulous observation and monitoring to prevent a relatively minor AE becoming a serious AE. Patients presenting with BEs are a complex patient population who must not be prescribed "sedate and forget" medication orders. These patients must be cared for, in monitored and high visibility areas of the ED, by staff with expertise in airway management.

Given the large number of elderly patients (i.e. >65 years) who present to EDs, this group was underrepresented in this study. This suggests that parenteral sedation may not be widely used in this population. This result is consistent with current best practice recommendations.[3,4] Also consistent

with previous literature, organic disorders, such as underlying dementia were found to be the most common diagnosis in elderly patients who required parenteral sedation.[24] In line with previous studies, lower doses of parenteral sedation were administered to the elderly patients with BEs.[25] However, there was a marked variation in the choice of initial sedative medication. Although not quite reaching statistical significance there was a trend towards AEs being more prevalent in patients aged > 65 years compared to patients aged < 65 (8/31; 25.8% versus 66/516; 12.8%; p =0.0544).

Given the vulnerability of elderly patients to AEs, our findings support the need to monitor these patients carefully following parenteral sedation. A larger study examining the use of parenteral sedation among elderly patients will be required to determine the incidence and risk factors (e.g. polypharmacy) that are associated with sedation-induced AEs.

There are limitations in the generalisability of our data. Although these data are not necessarily representative of the practice Australia-wide, they provide unique insights into prescribing patterns for the management of BEs. Although every effort was made to encourage clinical staff to enrol eligible patients into the study, the busy nature of EDs makes it challenging for all clinical staff to stay committed to the process of patient recruitment. Patients may have been missed and had no data collected, resulting in a truly consecutive sample not being achieved and selection bias might have been introduced. It was also not possible to retrospectively determine the number and nature of the patients not enrolled as sedation for management of acute agitation is not specifically classified in medical records. In addition, some minor AEs may not have been recorded. Whilst higher sample numbers will lead to smaller confidence intervals and increase the chance of detecting rare AEs, the current sample size which afforded 13.5% AEs is within the estimated range and appears to have captured the most common types of AE related to the parenteral sedation in this setting.

Other limitations of this study include those associated with observational studies such as the absence of randomisation and blinding. However, the naturalistic design of this multicentre observational study provides a clear description of current parenteral sedation practice in the participating EDs and enables assessment of AEs in a broad group of patients (e.g. inclusive of elderly patients). This study sought to document AEs associated with parenteral sedation but cannot make recommendations regarding the dose-response relationship between specific sedative medications and AEs.

Conclusion

Overall, the participating EDs provided safe pharmacological management for BEs. The current findings suggest the parenteral sedation practice has changed in accordance with the emerging new evidence from clinical studies. As all patients receiving parenteral sedation for BEs are at risk for AEs, ongoing monitoring of vital signs after parenteral sedation should be a standard protocol in all EDs.

Table 1. Characteristics of participants

	Total (n=547)	**Monotherapy (n=472)**	**Combination therapy (n=75)**	**P value**
Age, years				0.78
≤ 30	188 (34.3)	161 (34.1)	27 (36.0)	
31-65	328 (60.0)	283 (60.0)	45 (60.0)	
> 65	31 (5.7)	28 (5.9)	3 (4.0)	
Male, n (%)	346 (63.3)	298 (63.1)	48 (64.0)	0.89
ICD-10 category, n (%)				0.31
Mental illness	216 (39.5)	190 (40.3)	26 (34.7)	
Intoxication (drugs and/or alcohol)	263 (48.1)	221 (46.8)	42 (56.0)	
Organic illness	68 (12.4)	61 (12.9)	7 (9.3)	
Drug overdose at presentation	49 (9.0)	46 (9.7)	3 (4.0)	0.11
Usual psychotropic medications prior to presentation, n (%)	211 (38.6)	187 (39.6)	24 (32.0)	0.21
Benzodiazepines	73 (13.3)	65 (13.8)	8 (10.7)	0.46
SSRI or SNRI	65 (11.9)	56 (11.9)	9 (12.0)	0.97
Atypical antipsychotics	109 (19.9)	95 (20.1)	14 (18.7)	0.77

	Total (n=547)	Monotherapy (n=472)	Combination therapy (n=75)	P value
Typical antipsychotics	14 (2.6)	13 (2.8)	1 (1.3)	0.71
Prescription opioids*	57 (10.4)	53 (11.2)	4 (5.3)	0.12
Alcohol intoxicated, n (%)	236 (43.1)	206 (43.6)	30 (40.0)	0.55
Illicit drug intoxicated, n (%)	247 (45.2)	204 (43.2)	43 (57.3)	0.02
Need for mechanical restraint, n (%)	230 (42.0)	192 (40.7)	38 (50.7)	0.10
Need for additional parenteral sedation within the first 60 minutes after the initial dose regimen, n (%)	71 (13.0)	62 (13.1)	9 (12.0)	0.79

ICD-10=International Classification of Diseases; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin noradrenalin-reuptake inhibitor

*Prescription opioids included oxycodone, hydrocodone, morphine, codeine, fentanyl, methadone, hydromorphone

Table 2. Initial choice of sedation regimens for all patients

Choice of sedative medications	Total cases (n=547)	Median initial dose† (range), mg	Route of administration, n (%)	
			IV (n=110)	IM (n=437)
Monotherapy	**472 (86.3)**	**-**	**82 (74.5)**	**390 (89.2)**
droperidol	381 (69.7)	10 (1-30)	38 (34.6)	343 (78.5)
midazolam	54 (9.9)	5 (1-10)	38 (34.5)	16 (3.7)
olanzapine	26 (4.8)	10 (2.5-10)	0 (0.0)	26 (5.9)
haloperidol	5 (0.9)	2.5 (2-10)	1 (0.9)	4 (0.9)
diazepam	4 (0.7)	7.5 (2.5-10)	2 (1.8)	2 (0.5)
lorazepam	1 (0.2)	2*	0 (0.0)	1 (0.2)
propofol	1 (0.2)	70*	1 (0.9)	0 (0.0)
Combination therapy	**75 (13.7)**	**-**	**28 (25.5)**	**47 (10.8)**
droperidol + midazolam	36 (6.6)	10 (2.5-20) + 5 (2-10)	13 (11.8)	23 (5.3)
olanzapine + midazolam	9 (1.6)	10 (5-10) + 5 (2-10)	1 (0.9)	8 (1.8)
droperidol + olanzapine	8 (1.5)	10 + 10*	0 (0.0)	8 (1.8)
droperidol + diazepam	6 (1.1)	7.5 (5-10) + 7.5 (5-10)	3 (2.7)	3 (0.7)
haloperidol + midazolam	5 (0.9)	20 (2.5-20) + 5 (1-10)	4 (3.6)	1 (0.2)
droperidol + ketamine	3 (0.5)	10 (10-20) + 200 (30-200)	1 (0.9)	2 (0.5)
ketamine + midazolam	3 (0.5)	60 (40-150) + 5 (5-10)	3 (2.7)	0 (0.0)
droperidol + clonazepam	2 (0.4)	4.75 (2-7.5) + 2.25 (0.5-4)	2 (1.8)	0 (0.0)
droperidol + lorazepam	1 (0.2)	10 + 2*	0 (0.0)	1 (0.2)
ketamine + clonazepam	1 (0.2)	400 + 4*	0 (0.0)	1 (0.2)

ketamine + morphine	1 (0.2)	10 + 1*	1 (0.9)	0 (0.0)

IV= intravenous; IM= intramuscular

† This was the total initial dose and may have been administered incrementally over the first 15 minutes.

* This was the actual dose administered to the patient, no other dose was observed.

Table 3. Frequency and nature of adverse events across all study sites

	Total (n=547)
Number of patients with reported events, n (%)	74 (13.5)
Respiratory AEs	
Oxygen desaturation	30 (5.5)
Airway obstruction	13 (2.4)
Hypoventilation	4 (0.7)
Cardiovascular AEs	
Bradycardia	9 (1.6)
Hypotension	8 (1.6)
Prolonged QTc	5 (0.9)
Tachycardia	1 (0.2)
Others	
EPSE	5 (0.9)
Vomiting	2 (0.4)
Urinary retention	2 (0.4)
Dry mouth	1 (0.2)
Fall	1 (0.2)
Anaphylaxis	1 (0.2)

	Total (n=547)
Total cases of AEs	82 (15.0)

AE= adverse event; EPSE= extrapyramidal side effects; QTc= corrected QT interval

Table 4. Initial choice of sedation regimens for patients aged > 65 years

Choice of sedative medications	Total cases (n=31)	Median initial dose (range)†, mg	Route of administration, n (%)	
			IV (n=15)	IM (n=16)
Monotherapy	**28 (90.3)**	**-**	**13 (86.6)**	**15 (93.8)**
droperidol	15 (48.4)	5 (2.5-15.0)	2 (13.3)	13 (81.3)
olanzapine	5 (16.1)	5 (2.5-10.0)	5 (33.3)	0 (0.0)
midazolam	5 (16.1)	2 (1.0-3.0)	5 (33.3)	0 (0.0)
haloperidol	3 (9.7)	2.5 (2.0-5.0)	1 (6.7)	2 (12.5)
Combination therapy	**3 (9.7)**	**-**	**2 (13.4)**	**1 (6.2)**
droperidol + midazolam	1 (3.2)	10 + 10	0 (0.0)	1 (6.2)
droperidol + clonazepam	1 (3.2)	2 + 0.5	1 (13.4)	0 (0.0)
haloperidol + midazolam	1 (3.2)	2.5 + 1	1 (13.4)	0 (0.0)

IV= intravenous; IM= intramuscular

† This was the total initial dose and may have been administered incrementally over the first 15 minutes.

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