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Pharmacology in Emergency Medicine

KETAMINE USE FOR ACUTE AGITATION IN THE EMERGENCY DEPARTMENT

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Abstract—Background: Emergency physicians regularly encounter agitated patients. In extremely agitated and violent patients, the onset of many traditional medications is relatively slow and often requires additional medication. Ketamine is frequently used in emergency departments (EDs) for procedural sedation and intubation, but has recently been suggested as a treatment for acute agitation. **Objectives:** We sought to examine the use of ketamine in the treatment of acute agitation in an ED setting, including vital sign changes as a result of this medication. **Methods:** This is a structured review of an historical cohort of patients over 7 years at two university EDs. Patients were included if they received ketamine as treatment for acute agitation. **Abstracted data included** age, vital signs including hypoxia, any additional medications for agitation, and alcohol/drug intoxication. **Results:** Ketamine was administered for agitation on 32 visits involving 27 patients. Preadministration systolic blood pressure was 131 ± 20 mm Hg, with an average postadministration increase of 17 ± 25 mm Hg. The average baseline heart rate was 98 ± 23 beats/min, with an average increase of 8 ± 17 beats/min. No patients became hypoxic; 62.5% of patients required additional calming medication. Alcohol or drug intoxication was present in 40.6% of patients. **Conclusions:** We found ketamine was used rarely, but had few major adverse effects on vital signs even in a population with 21.9% alcohol intoxication. However, a high proportion (62.5%) of patients required additional

pharmacologic treatment for agitation, implying that administering ketamine is useful only for initial control of severe agitation. © 2015 Elsevier Inc.

Keywords—ketamine; agitation; aggression; control; vital signs

INTRODUCTION

Emergency physicians regularly encounter agitated patients in the emergency department (ED) (1–11). Causes of ED-based agitation are numerous, ranging from psychosis to intoxication (2–5,8). Although verbal de-escalation is recommended as first-line treatment, in some cases this can be ineffective and medication administration may be required to prevent these patients from harming themselves or others (10,12). However, many of these medications have a relatively slow onset, require empiric dosing, and often require additional medication for calming (10,13).

Ketamine is a dissociative agent acting through antagonism of glutamate *N*-methyl-D-aspartate receptors, which causes a trance-like state resulting in analgesia and amnesia (14). It is frequently used in EDs for procedural sedation as well as an induction agent for intubation, but has only recently been proposed as a treatment for agitation. Dissociative anesthesia occurs in 1–2 min

This study was approved by the institutional review board of the University of California, San Diego prior to data collection.

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intravenously and approximately 3 min in intramuscular administration (14,15).

In particular, ketamine has been proposed as an alternative to traditional antipsychotic treatment in the treatment of severe acute agitation (13,16,17). The American College of Emergency Physicians' White Paper on Excited Delirium Syndrome describes the benefits of ketamine as a fast-acting medication in agitated and violent patients with a low rate of side effects (18). The rapid onset of ketamine, under 5 min, compares favorably to haloperidol and droperidol, in which peak sedation can take more than 20 min (19,20). Most of the literature focuses on the traditional uses of ketamine for procedural sedation primarily involving children or induction for intubation. Little published research has been done on its use for the treatment of acute agitation in EDs, though one prehospital case series has shown significant decreases in oxygen saturation after administration (21).

The oxygen desaturations in this case series are puzzling, particularly because ketamine is thought by most emergency physicians to have few effects on vital signs. However, ketamine has been noted to worsen tachycardia and hypertension in nonagitated patients, and may be a mild respiratory depressant at high doses, with respiratory drive depressed approximately 15–22% (15,22,23). Post administration, dysphoric emergence phenomena have been reported to occur in 10–20% of adult patients sedated with ketamine, though these are often mild and can be treated with low doses of midazolam (21). Adjunctive use of benzodiazepines may be dispreferred in children, however, studies have shown no difference between midazolam and placebo groups in rates of recovery agitation and that benzodiazepines may increase the risk of adverse airway events in children (22,24).

Objectives

The purpose of this study is to examine the efficacy and safety of ketamine in the treatment of acute agitation in an ED setting. Given a recent report that ketamine use in the prehospital setting was associated with a surprising number of oxygen desaturations, the primary measurement of interest was any increases or decreases in vital signs after ketamine, particularly oxygen saturation (21).

MATERIALS AND METHODS

Study Design and Setting

This is an historical cohort study at two university EDs, one urban academic teaching hospital, and one suburban community hospital. Combined, these EDs treat approximately 65,000 patients per year. This study was approved by the local institutional review board prior to data collection.

Selection of Participants

The cohort was identified by a keyword search of the electronic medical record (EMR) for all patients who received ketamine between September 15, 2004 and June 6, 2012. Patients were included if ketamine was administered as treatment for acute agitation. Agitation was defined, following recent American Association for Emergency Psychiatry BETA project guidelines, as “an extreme form of arousal that is associated with increased verbal and motor activity” (25). This definition was operationally adapted for use by including situations where the patient was noted to be physically aggressive with staff, require restraints, or have increased verbal/motor activity interfering with treatment. Patients were excluded if they received ketamine for any other reason, including procedural sedation or intubation, or if the chart was irretrievable.

The following variables were queried from the EMR: age, sex, and chief complaint. The following data were then abstracted by blinded research associates: patient vital signs (heart rate, blood pressure, respiratory rate, and oxygen saturation), route/dose/time of ketamine administration, previous administration of antipsychotics or benzodiazepines, additional calming medication within 3 h, alcohol levels measured via serum alcohol/breathalyzer, and urine toxicology lab results when available. If available, preadministration vital signs were recorded as close to the initial administration of ketamine as possible. If available, postadministration vitals were recorded for both the lowest and highest values of a particular vital sign parameter that were recorded within 4 h of administration. Additional calming medication was defined as additional antipsychotics, benzodiazepines, or ketamine administered for agitation within 3 h of the initial dose of ketamine. Although 3 h is not based on the half-life of ketamine, this figure has been used in other agitation investigations of this type (26–29). All records were evaluated by a minimum of three researchers who were trained on use of the EMR. At least 2 research assistants evaluated the EMR for each patient visit and selected those cases where ketamine was given for agitation; once all researchers had completed their review, the results were compared. Full consensus between the researchers was required for inclusion. Patients selected for inclusion subsequently had their EMR further evaluated for return to the ED for exacerbation of any psychiatric issues after administration of ketamine.

Data Collection and Processing

All data were entered into a standardized computer worksheet using Excel 2010 (Microsoft, Redmond, WA), and then checked for nonsensical values. Change in vital signs within 4 h after administration of ketamine was calculated

relative to the baseline vital sign preadministration within each patient to prevent small changes in baseline vital signs from skewing the analysis across patients. Four hours postmedication administration was chosen, as this has been used in other investigations of this type and is approximately equal to two half-lives of ketamine ($t_{1/2} = 2.17$ h) (23,26–29). Hypoxia after administration of ketamine was defined as an oxygen saturation of <90%.

Outcome Measures

The primary outcome measures were change in vital signs postadministration and the need for any additional calming medication. Vital sign changes were calculated within a particular patient, as noted above.

Primary Data Analysis

Descriptive statistics were used to evaluate patient characteristics such as age, gender, change in vitals, ketamine dose, and proportions of patients who received additional calming medication within 3 h.

RESULTS

Over the study period, 459 patients who received ketamine in the ED were identified. Thirty-two cases involving 27 patients met study inclusion and exclusion criteria and were subjected to further analysis. The remaining 427 patient visits received ketamine for non-agitation-related causes, primarily for procedural sedation or induction of intubation. One autistic, nonverbal patient who was uncooperative with treatment received ketamine on five separate visits. The age range of the study group was from 9 to 77 years (average age of 35 ± 16 years; 20 males). Weight was recorded in five patient visits. Discharge diagnoses, age, and gender for each patient are listed in Table 1.

A total of 17 patient visits received intramuscular (i.m.) ketamine, and 15 received intravenous (i.v.) administration. In 18 (56.2%) cases, a patient received medication for agitation prior to being administered ketamine, most often a combination of an antipsychotic and a benzodiazepine. On 20 patient visits (62.5%), additional calming medication was utilized, most often additional ketamine. In eight (25%) visits, both pre- and postadministration medication was required. Thirteen patients intoxicated with alcohol or other substances (40.6%) required additional calming medication at a higher rate than those who were not (84.6% vs. 47.4%). A summary of medication and intoxication can be found in Table 2. In no cases were dysphoric emergence reactions noted, and in no cases did patients return to the ED for noted exacerbations of psychiatric conditions due to ketamine.

Table 1. Summary of Patient Gender, Age, and Discharge Diagnosis

Case	Gender	Age, Years	Discharge Diagnosis*
1	M	10	Agitation (autism/tuberous sclerosis)
2	F	9	Head trauma
3	M	36	Alcohol intoxication
4	M	31	Polysubstance intoxication
5	M	20	Leg pain (autism)
6	M	34	Polysubstance intoxication
7†	F	24	Ovarian cyst (autism)
8	M	40	Primary psych & polysubstance intoxication
9	M	41	Polysubstance intoxication
10	M	28	Amphetamine intoxication
11†	F	24	Finger pain (autism)
12†	F	24	Ovarian cyst (autism)
13†	F	24	Ovarian cyst (autism)
14	M	56	Head trauma (developmental delay)
15	M	49	Anticholinergic delirium
16	M	50	Seizure
17†	F	24	Ovarian cyst (autism)
18	M	53	Amphetamine intoxication
19	F	30	Suicide attempt
20	F	40	Chronic pain
21	F	19	Polysubstance intoxication
22	M	12	Antipsychotic medication change (autism)
23	M	53	AIDS-related encephalitis
24	M	31	Chronic pain
25	M	34	Primary psych
26	M	77	Dementia
27	M	53	Primary psych & cocaine intoxication
28	F	37	End-stage renal disease
29	F	26	Primary psych & alcohol intoxication
30	M	26	Alcohol intoxication
31	F	71	Dementia
32	M	47	Alcohol intoxication

* Parentheses after the diagnosis contains conditions indicated to be exacerbating agitation or impeding treatment.

† These five cases represent the same patient on different visits to the emergency department.

There were sufficient data to evaluate postadministration change in systolic blood pressure (SBP) in 22 visits with an average preadministration SBP of 131 ± 20 mm Hg. Within 4 h of administration, the highest recorded SBP for each patient showed an average increase of 17 ± 25 mm Hg from the patient's baseline. The lowest recorded SBP in the same time period showed an average drop of 14 ± 24 mm Hg. Change in heart rate was evaluated in 25 cases; the average preadministration heart rate was 98 ± 23 beats/min. The average highest increase from baseline was 8 ± 17 beats/min, and the largest decrease was 10 ± 18 beats/min. Twenty-two cases provided oxygen saturation data in which the preadministration average was $98 \pm 2\%$. Postadministration average highest increase was $1.1 \pm 1.7\%$, and average largest decrease was $0.6 \pm 2.2\%$. No patients became hypoxic; the lowest oxygen saturation after administration was 94%. A summary of change in SBP and heart rate can be found in Table 3.

Table 2. Medication Administered and Urine Toxicology/Breathalyzer Results

Case	Prior Medication	Initial Ketamine Dose	Additional Medical Intervention	Intoxication†
1		150 mg i.m.	+00:50 Ketamine 150 mg i.m.	
2		40 mg i.m.	+00:13 Ketamine 40 mg i.m. +00:35 Ketamine 40 mg i.m. +00:50 Ketamine 60 mg i.m. +01:02 Midazolam 2 mg i.m.	
3		200 mg i.m.		BAL 245 mg/dL
4		160 mg i.v.	+01:00 Olanzapine 10 mg i.m.	BAL 119 mg/dL Benzodiazepines "Mushrooms"
5	–00:17 Lorazepam 2 mg i.m.	200 mg i.m.		
6		200 mg i.m.		
7		100 mg i.m.	+00:10 Ketamine 100 mg i.m. +00:30 Haloperidol 5 mg i.v. +00:45 Midazolam 2 mg i.v.	"Alcohol" "Cocaine"
8	–00:44 Haloperidol 10 mg p.o. –01:41 Lorazepam 1 mg p.o. –02:47 Haloperidol 5 mg p.o.	60 mg i.v. 320 mg i.m.	+00:27 Ketamine 60 mg i.v. +00:13 Haloperidol 5 mg i.v. +00:13 Lorazepam 2 mg i.v.	Cocaine Opiates
9		140 mg i.v.	+00:07 Haloperidol 5 mg i.v. +02:18 Midazolam 5 mg i.v.	BAL 344 mg/dL Oxycodone
10		400 mg i.v.	+00:40 Diazepam 10 mg i.v. +01:22 Midazolam 5 mg i.v.	Amphetamines Benzodiazepines
11	–01:17 Clonazepam*†	200 mg i.m.		
12		200 mg i.m.	+01:25 Ketamine 100 mg i.v.	
13		200 mg i.m.	+00:25 Ketamine 100 mg i.m. +02:50 Ketamine 200 mg i.m.	
14	–01:11 Lorazepam 2 mg i.v. –01:22 Haloperidol 5 mg i.v.	100 mg i.v.		
15	–00:13 Droperidol 2.5 mg i.v. –00:54 Haloperidol 5 mg i.v. –00:54 Midazolam 4 mg i.v. –00:54 Lorazepam 2 mg i.v.	100 mg i.v.		
16	–00:22 Midazolam 2 mg i.m. –00:20 Midazolam 2 mg i.m.	120 mg i.v.		
17	–01:10 Lorazepam 2 mg i.v. –01:40 Lorazepam 2 mg i.v.	100 mg i.v.		
18	–00:20 Lorazepam 2 mg i.m. –00:52 Haloperidol 5 mg i.m. –01:21 Lorazepam 2 mg i.m. –02:15 Diphenhydramine 50 mg i.m. –02:15 Lorazepam 2 mg i.m. –02:32 Haloperidol 5 mg i.m.	50 mg i.v.	+02:18 Ketamine 30 mg i.v. +02:48 Ketamine 20 mg i.v.	"Methamphetamine"
19	–00:03 Haloperidol 10 mg i.m. –00:03 Lorazepam 2 mg i.m. –00:03 Diphenhydramine 50 mg i.m. –00:28 Lorazepam 2 mg i.m. –00:55 Clozapine 100 mg p.o.	200 mg i.v.		
20	–00:15 Lorazepam 2 mg i.v. –00:45 Droperidol 2.4 mg i.m. –00:45 Lorazepam 2 mg i.m.	300 mg i.m.		
21	–00:05 Midazolam 10 mg i.m.*	200 mg i.m.		BAL 233 mg/dL Methamphetamines
22	–00:18 Droperidol 2.25 mg i.m. –00:18 Lorazepam 2 mg i.m.	400 mg i.m.	+01:04 Lorazepam 2 mg i.v. +01:52 Lorazepam 3 mg i.v.	
23		200 mg i.m.	+00:34 Lorazepam 2 mg i.v.	
24	–00:56 Lorazepam 1 mg i.v. –01:56 Droperidol 1.25 mg i.v.	50 mg i.v.		
25	–00:00 Lorazepam 2 mg i.v. –00:16 Droperidol 2.25 mg i.v. –00:16 Lorazepam 2 mg i.v. –00:32 Lorazepam 1 mg i.v.	100 mg i.v.	+02:24 Ketamine 100 mg i.v. +02:24 Diazepam 10 mg i.v.	"Soma/Ambien overdose"
26	–00:10 Lorazepam 1 mg i.v.	100 mg i.v.	+00:15 Ketamine 50 mg i.v.	
27	–00:05 Lorazepam 2 mg i.m.	150 mg i.m.	+00:20 Lorazepam 1 mg i.m.	Cocaine
28		50 mg i.m.		

(Continued)

Table 2. Continued

Case	Prior Medication	Initial Ketamine Dose	Additional Medical Intervention	Intoxication†
29		160 mg i.m.	+00:41 Ketamine 240 mg i.m.	BAL 079 mg/dL
30		150 mg i.m.	+01:29 Droperidol 1.25 mg i.v. +00:40 Lorazepam 2 mg i.v. +01:10 Ketamine 50 mg i.v. +01:44 Haloperidol 5 mg i.v. +01:56 Lorazepam 2 mg i.v.	
31	–01:56 Haloperidol 5 mg i.m. –01:56 Lorazepam 2 mg i.m.	40 mg i.v.	+00:15 Ketamine 20 mg i.v.	Oxycodone
32	–01:18 Droperidol 2.25 mg i.v. –01:56 Lorazepam 2 mg i.v. –02:41 Haloperidol 5 mg i.m. –02:53 Lorazepam 2 mg i.m.	100 mg i.v.	+00:07 Ketamine 100 mg i.v. +00:27 Midazolam 10 mg i.v. +01:22 Midazolam 1 mg/h i.v. +01:27 Midazolam 5 mg i.v. +01:37 Midazolam 5 mg i.v. +01:47 Midazolam 5 mg i.v.	BAL 284 mg/dL

BAL = blood alcohol level.

“–” and “+” for prior medication and additional medical intervention indicate time in relation to initial ketamine dose.

Quotation marks indicate physician-reported patient use/intoxication.

* Medication reported to be given shortly prior to arrival. Time indicated is triage time in relation to ketamine administration time.

† Clonazepam dose not indicated.

DISCUSSION

Several case reports have documented the potential usefulness of ketamine in severe agitation (13,21,30,31). The putative advantages of this medication for agitation include rapid onset, the preservation of airway reflexes,

and the ability to administer either i.m. or i.v., which may itself be particularly useful if i.v. access is not easily obtained. In addition, sedation is often achieved reliably with one dose (23). Compared to other agents, the half-life of ketamine is relatively short, potentially allowing more rapid disposition of agitated patients (23).

Table 3. Patient Vitals Pre- and Postadministration of Ketamine

Case	Ketamine Dose (mg)	Systolic Blood Pressure (mm Hg)			Heart Rate (Beats/min)		
		Predose	Postdose (High)	Postdose (Low)	Predose	Postdose (High)	Postdose (Low)
1	150				86	104	104
2	40	112	108	108	93	102	102
5	400	124	179	172	80	91	70
7	60	128	90	90	121	115	115
8	320	120	151	113	120	98	78
9	140	137	137	114	119	107	98
11	200				72	114	108
12	200	148	155	107			
13	200				107	122	88
14	100	107	149	104	59	86	56
15	100	134	118	118	112	124	117
16	120				111	109	85
17	100	133	135	97	78	98	69
18	50	119	145	116	87	106	78
19	200	117	136	131	99	135	107
20	300	155	161	115	85	77	64
23	200	101	169	126	116	132	98
24	50	111	117	117	86	80	80
25	100	137	157	121	118	123	94
26	100	143	175	125	70	97	82
27	150	195	185	140	75	112	63
28	50	132	162	135	94	99	80
29	160	138	151	114	147	131	125
30	150	134	144	114	103	95	65
31	40	131	184	91	76	76	69
32	100	120	144	101	150	143	113

Postdose vitals contain highest and lowest recorded values within 4 h of ketamine administration. Cases where vitals were not charted are not included; blank spaces are indicative of that vital not being charted in that specific case.

Potential disadvantages of ketamine include the fact that patients who are in a dissociative state are unable to participate in their own care (4,5,10). Ketamine also does not treat the underlying cause of agitation, and if the etiology of the agitation persists, patients may require multiple doses of additional calming medications. In this study, for instance, patients with substance/alcohol intoxication needed calming medication at higher rates. Finally, there is evidence from at least one double-blind placebo-controlled trial that subanesthetic doses of ketamine may worsen psychosis, which may make use of this medication inappropriate in patients who have a psychiatric cause of their illness (32).

Little has been published on the use of ketamine for agitation. Roberts & Geeting described in a case study the successful treatment of an acutely agitated and violent patient with i.m. ketamine without major adverse effects, and a case series by Le Cong et al. reported that ketamine provided adequate sedation in agitated psychiatric patients who had not responded to treatment with benzodiazepines, without any major adverse effects (13,30). However, these report did not follow long term to confirm any worsening of psychosis after administration.

Much of the ED literature has focused on changes in vital signs. Burnett et al. report on several patients administered ketamine in the prehospital setting who had surprising decreases in oxygen saturations (21). In terms of other vital sign parameters, increases in blood pressure and heart rate are frequently seen, but are rarely clinically significant (15). This is true in the study above as well, in which increases in blood pressure and heart rate are frequently present but not noted as significant. In four cases, the highest recorded blood pressure after ketamine administration was lower than the predose SBP; this trend was also seen in heart rate in eight cases. In these cases, the effect of calming during an agitated episode on vitals may outweigh any changes induced by ketamine. Additionally, in no cases were significant changes in oxygen saturation noted, and no patients became hypoxic, contrary to the results seen in prehospital literature.

Slightly over half of the cases (62.5%) required additional medication for agitation after receiving ketamine, suggesting ketamine alone in the dose used is often not enough to resolve agitation. This is not unexpected as typically, ketamine was being used to gain rapid and safe control of severely agitated patients to facilitate a more structured medical evaluation. As ketamine has not been proposed specifically as a treatment for agitation from undertreated psychiatric illnesses or even sympathomimetic drug intoxication, but rather as a means to permit initial work-up of an agitated patient, it is perhaps not surprising to find that the majority of patients required additional medications.

Of interest, there were eight cases (Table 2: patients 14, 15, 16, 18, 19, 20, 24, and 25) where multiple doses of an antipsychotic or a benzodiazepine were given without resolution of agitation. Once given ketamine, these patients either did not require additional calming medication at all or did not need it within 3 h. Two of these patients, 18 and 19, received a “B-52” consisting of haloperidol, lorazepam, and diphenhydramine, traditionally thought to be extremely effective in sedating agitated patients, yet still required ketamine to resolve agitation. This may highlight ketamine’s usefulness with severely agitated patients, as well as introducing ketamine as a potential alternate medication for patients nonresponsive to traditional pharmacological interventions.

Limitations

The retrospective, case series nature of this study may suffer from selection bias, as patients were not prospectively randomized and enrolled in treatment arms. The small patient population of the study also limits the ability to generalize to other populations. Incomplete charting led to a lack of vitals for several of the patients, decreasing our ability to further evaluate ketamine’s reported effects on vital signs. A patient’s weight is not routinely included in ED charts, and so precludes further evaluation of the appropriateness of dosing in most cases.

CONCLUSIONS

Relative to other pharmacologic treatments for agitation, ketamine is infrequently used in the ED. We found that ketamine was used without any major adverse effects on vital signs, even in a population with 21.9% alcohol intoxication. However, a high proportion (62.5%) of patients required additional pharmacologic treatment for their agitation, implying that ketamine itself is not an ideal treatment for the underlying cause of agitation, but rather a means of initial management of severe agitation. A prospective study is warranted to further clarify the safety and efficacy of the use of ketamine in this situation.

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ARTICLE SUMMARY**1. Why is this topic important?**

Agitation is a common problem encountered in emergency departments (EDs) and may require pharmacological intervention if other attempts at resolution are unsuccessful.

2. What does this study attempt to show?

This study evaluates the effect of ketamine on patient vitals when used as a means of sedation for agitated patients in EDs.

3. What are the key findings?

Ketamine was used without any major adverse effect on vital signs. 62.5% of patients required additional calming medication within 3 h.

4. How is patient care impacted?

When used as sedation for agitation, ketamine is not associated with vital sign changes. As ketamine is relatively short acting, additional medication may be required to treat the cause of agitation.