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Selected Topics: Toxicology

KETAMINE ABUSERS PRESENTING TO THE EMERGENCY DEPARTMENT: A CASE SERIES

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□ **Abstract—Ketamine hydrochloride, familiar to emergency physicians as a dissociative anesthetic, has been abused as a hallucinogen for almost 30 years. The drug produces effects similar to those of phencyclidine but with a much shorter duration of effect. Since 1996, an increasing number of patients have presented to Connecticut Emergency Departments (EDs) after the intentional abuse of ketamine. Because the medical literature contains almost no information on the consequences of ketamine abuse, we have compiled a series of ketamine abusers presenting to the ED. Among the 20 patients in this series, common presenting complaints included anxiety, chest pain, and palpitations. Tachycardia was the most common physical examination finding Nystagmus, a common findin after phencyclidine use, was seen in only three cases. The most frequent complications after ketamine abuse were severe agitation and rhabdomyolysis. The symptoms of ketamine intoxication appear to be short-lived, with 18 of the 20 patients discharged from the ED within 5 h of presentation. Emergency physicians should include ketamine in the differential diagnosis of drug- or toxin-induced hallucinations. Methods for detecting this drug in biologic fluid are reviewed as are treatment recommendations for managing the patient who presents to the ED after abusing ketamine.**

□ **Keywords—ketamine; hallucinogen; case series; emergency department**

INTRODUCTION

Ketamine hydrochloride was introduced as a general anesthetic in the late 1960s as an analogue of phencyclidine (PCP), which had proved to be too toxic for human use (1). Ketamine was initially well received because it produced excellent anesthesia without the respiratory and cardiovascular depression that occurs with other agents (2). Unfortunately, a frequent complication of ketamine anesthesia use was the occurrence of disturbing hallucinations upon awakening ("emergence reactions") (3). This limited the drug's clinical usefulness, and by the early 1970s, it had been replaced by other anesthetics (2). Today, ketamine is used primarily to induce dissociative sedation for brief procedures that require the patient (usually a child) to be absolutely still (4). It is used in a similar manner by veterinarians (5).

Reports of ketamine abuse began to appear in the medical literature soon after its introduction into clinical practice (6,7). The drug produces effects similar to those of PCP but with a much shorter duration of action (3). Early reports of ketamine abuse involved people who had easy access to the drug, such as health care workers and animal trainers (6,7). In 1996, the Connecticut Poison Control Center began receiving an increasing number of calls from emergency physicians seeking treatment advice for patients who presented to the emergency

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department (ED) after ketamine abuse. A literature search by the authors found almost no published data on the complications of ketamine abuse.

The objective of this study was to prospectively collect data on patients presenting to Connecticut EDs after having abused ketamine. Based on our observations, we make recommendations for anticipating and treating the complications of ketamine abuse.

MATERIALS AND METHODS

This was a prospective observational case series of ketamine abusers presenting to Connecticut EDs in 1997. When the Connecticut Poison Control Center was notifie of such a patient, one of the authors contacted the treating physician to obtain more information (described below). Patients were included in this case series only if the treating physician was available to review the ED visit and if all the information outlined below was available.

Demographic data included patient age and sex. Elements of the patient's history included the dose of ketamine used (if known), the route of ketamine administration, and the time of administration. Other drugs that the patient admitted using were recorded, as was any complaint the patient had upon presenting to the ED.

Physical examination data included a complete set of vital signs, a description of the patient's mental status, and the presence of any ocular findings including nystagmus. Any other positive finding noted by the treating physician were also recorded.

Repeat calls were made by one of the authors to document the results of any laboratory studies as well as the progression of the patient's signs and symptoms. Any treatment given to the patient, including i.v. fluid and all medications, was recorded. Final disposition as well as total time in the ED were noted.

Confirmatio of ketamine use by testing of urine or blood was not required for entry into the study. Testing for other drugs of abuse also was not required. The results of such testing were documented when it was done.

RESULTS

During 1997, 27 cases of self-reported ketamine abuse were called in to our poison control center from Connecticut EDs. Twenty of the 27 (74%) met criteria for inclusion in the study. Two were excluded because the treating physician was unavailable, and in fiv other cases, information on the patient was incomplete. The 20 patients who made up our study population consisted of 11 men and 9 women, ages 15–40 years old. Almost all the subjects were Caucasian and lived in either suburban or rural parts of the state.

Table 1. Signs and Symptoms in Ketamine Abusers

Presenting Complaints		Physical Examination	
Complaint	Number (% total)	Finding	Number (% total)
No complaint	10 (50%)	Tachycardia	12 (60%)
Anxiety	8 (40%)	Altered mental status	6 (30%)
Palpitations	3 (15%)	Slurred speech	5 (15%)
Chest pain	2 (10%)	Hallucinations	3 (15%)
Confusion	1 (5%)	Nystagmus	3 (15%)
Vomiting	1 (5%)	Mydriasis	3 (15%)
Memory loss	1 (5%)	Hypertension	2 (10%)

Eleven of the 20 patients stated that they had injected ketamine either subcutaneously or intramuscularly (i.m.), usually at a dose of 100–200 mg. Nine others stated that they had inhaled ketamine powder. One patient admitted to the simultaneous use of lysergic acid diethylamide (LSD), while another stated that he had used methamphetamine before injecting ketamine. The other patients denied concurrent or recent use of other drugs of abuse.

Presenting complaints and physical examination find ings are listed in Table 1. Half the patients were asymptomatic (i.e., they had no complaints) by the time they were evaluated in the ED. The unpleasant side effects after their use of ketamine that prompted them to seek medical attention had resolved before evaluation by an emergency department caregiver. Of the symptomatic patients, anxiety, chest pain, and palpitations were the most common presenting complaints.

Tachycardia was the most common abnormal findin on physical examination. More than half the patients with symptoms were still tachycardic (define as a heart rate greater than 100 beats per min) upon initial ED evaluation. Heart rate among these 12 patients ranged from 100−140 beats per min. Nystagmus, a commonly reported findin with PCP, was seen in only three patients. In all three cases, nystagmus was described as rotatory. Only three of the patients were still actively hallucinating at the time of their initial ED evaluation. All other patients were alert and oriented.

Emergency department treatment of these patients consisted largely of supportive care and sedation when needed. Five patients were agitated enough to require one or more doses of a benzodiazepine for sedation. Six patients received a single dose of activated charcoal because of concerns that an oral ingestion might be causing their altered mental status. Eighteen patients were released home after an observation period of 5 h or less in the ED. Two patients underwent prolonged observation. One patient with chest pain and hypertension

(blood pressure 180/100 mmHg) was treated with i.v. metoprolol and underwent a stress test 12 h after presentation (which was negative). A second patient displayed continued paranoid behavior several hours after presenting to the ED but was later found to have a prior history of schizophrenia. Median time in the ED for all patients was 3 h.

Complications known to occur with other stimulant drugs of abuse, such as hyperthermia, seizure, or dysrhythmia, did not occur in this group. Two mild cases of rhabdomyolysis were noted (creatine phosphokinase 200−600 IU/L), both in patients who were combative and required benzodiazepines for sedation. Both patients received i.v. hydration and were discharged home when their mental status normalized.

In most cases, no laboratory studies were done. Six patients had ethanol determinations, which were positive in two cases (40 and 120 mg/dL). Five patients had urine drug of abuse screens done (all immunoassays). Three patients were tested for the presence of phencyclidine, which is structurally similar to ketamine, and all three were negative. One drug screen detected the presence of cannabinoids, while another was positive for opiates.

DISCUSSION

Ketamine is a structural analogue of phencyclidine (1). Like PCP, ketamine combines analgesic and anesthetic effects without respiratory or cardiovascular depression (1). In the dissociative state induced by these drugs, the patient appears awake but is unaware of all sensory input (8). Whereas the signs and symptoms of PCP intoxication can remain for many hours, complete recovery is usually seen within 1 h after ketamine administration (3). Much like other short-acting, lipid-soluble anesthetics, the central nervous system effects of ketamine are terminated by redistribution from the brain into other tissues (9). Ketamine is extensively metabolized via demethylation by the hepatic P450 system to produce the active metabolite norketamine (10). The dissociative and anesthetic effects of ketamine have been attributed to its ability to antagonize N-methyl-D-aspartate (NMDA) receptors in the brain (11). Ketamine binds to a site (the PCP binding site) within the ion channel of the NMDA receptor to inhibit the influ of calcium, which results from glutamate binding (11). How this translates into a dissociative state is not fully understood.

The effects of ketamine are dose-dependent (1). Intramuscular doses of 3–4 mg/kg are typically used by emergency physicians to induce sedation (12). Such doses produce cardiovascular and respiratory stimulation. Paradoxically, higher doses can result in respiratory depression, loss of pharyngeal reflexes and even apnea (12). The subanesthetic doses used by ketamine abusers produce alterations in mood and body image, "out of body" experiences, sensations of floating vivid dreams, and illusions (13). Users refer to these effects as "visiting K-land" or "falling into the K-hole" (13).

Because it is difficul to synthesize, the ketamine that is used for illicit purposes is almost always diverted from legitimate sources, such as veterinary office (5). On the street, ketamine is known as K, Super K, and Special K (14). It is available as either a powder or a liquid. The powder can be snorted, smoked, or mixed into drinks. The liquid can be injected, applied to cigarettes, or consumed in other beverages. A typical recreational dose of ketamine is 100–200 mg (2,14,15). Data collected by the U.S. Drug Enforcement Administration indicates that ketamine abuse is increasing (14). As a result, seven states (California, Connecticut, New Mexico, Oklahoma, New Jersey, Illinois, and New York) have classifie ketamine as a category III controlled substance (14).

We found that ketamine was abused primarily by young people, most of whom were Caucasian. Approximately half reported injecting the drug whereas the other half stated that they had inhaled it. The effects of ketamine in this group appear to be short-lived, with half the patients being asymptomatic by the time of their ED evaluation. Those who were still symptomatic had complaints similar to those seen with other hallucinogenic drugs, including palpitations, anxiety, and chest pain (11). Most patients in this series were tachycardic, whereas nystagmus, a frequent findin with PCP, was rarely seen. Given the short duration of action of ketamine, it is possible that nystagmus had resolved in some of these patients before they presented to the ED. All patients in this series had a good outcome. Severe complications occasionally seen after the abuse of stimulant drugs (including PCP), such as dysrhythmia, seizure, and hyperthermia, did not develop in these patients. Two mild cases of rhabdomyolysis developed, as did fiv cases of agitation severe enough to warrant chemical sedation. All these patients did well with i.v. fluid and benzodiazepines.

Our results are similar to those of Dalgarno and Shewan, who in 1996 profile 20 ketamine abusers in Scotland (15). This, the only other case series dealing with ketamine abusers, is more of an epidemiologic profil of ketamine abusers. The authors found that ketamine abusers tended to be young, well-educated, and well-informed on the effects of the drug. Many users admitted to experimenting with a wide range of substances. Doses typically used were in the range of 100–200 mg, and patients reported that such doses reliably produced symptoms lasting 1 h or less. Adverse effects of ketamine reported by this group included unpleasant hallucinations and flashbacks sometimes occurring sev-

eral months after the last use of the drug. These people stated that there was less risk of unpleasant hallucinations if they used ketamine in a familiar, quiet environment. They reported progressive tolerance to the effects of ketamine but no withdrawal when the drug was stopped.

Ketamine can be detected in both plasma and urine (10). Gas chromatography with mass spectroscopy can be used to both detect and quantitate ketamine in either blood or urine (10). High-performance liquid chromatography (HPLC), a somewhat more widely available procedure, also can be used to quantitate concentrations of ketamine in blood (10). The results of either of these tests will not be back quickly enough to impact ED care of the suspected ketamine abuser. Several immunoassay tests are available for the detection of PCP in urine in less than 15 min (11). The structure of PCP is very similar to that of ketamine (10). At least one author has reported a case of a false-positive PCP immunoassay that was likely due to cross-reactivity with ketamine (16). In our series, three patients were tested with immunoassays that screened for PCP; all three were negative. Until more information becomes available, PCP immunoassays should not be considered reliable for the detection of ketamine in biologic fluids

Based on our experience, we offer the following treatment recommendations for evaluating ED patients who present after having abused ketamine. This diagnosis should be suspected in patients (especially young patients) who present with agitation, tachycardia, and either visual hallucinations or nystagmus. However, the absence of the latter two finding does not rule out the possibility of ketamine abuse. When laboratory confir mation of the diagnosis of ketamine abuse is critical to the patient's management (which is hardly ever the case), one of the aforementioned tests can be used.

Symptomatic patients are best managed with standard supportive care, as the effects of the drug are usually short-lived. Keeping the patient in a quiet environment, with a minimum of external stimuli, may prevent excessive agitation. Benzodiazepines should be used for sedation in agitated patients who are at risk for self-injury, hyperthermia, and rhabdomyolysis. Intravenous fluid should be given to agitated patients at a generous rate until laboratory testing has ruled out rhabdomyolysis. Activated charcoal is not necessary after ketamine abuse unless there is evidence that an oral coingestant may be contributing to the patient's symptoms. All patients must be observed until their vital signs and mental status have normalized. Symptoms not improving within 2 h of presentation should prompt a search for other drugs of abuse or another disease process. The differential diagnosis of drug- or toxin-induced hallucinations should include LSD, hallucinogenic mushrooms, amphetamine, PCP, ketamine, cocaine, anticholinergic drugs, and a variety of plants, especially morning glory, jimson weed, and nutmeg (11).

There are several significan limitations to the present study. First, we did not confir the presence of ketamine in these patients. It is possible that some of them either lied about what they had used or thought they had used ketamine when, in fact, they used a similar drug, such as PCP. Quantitating ketamine levels in this group may have demonstrated why some patients had a longer duration of symptoms, or more severe symptoms, than others. In addition, we did not require that the patients be tested for the presence of other drugs of abuse or alcohol. At least two of our patients had been drinking alcohol, and two of the fiv patients who were tested for drugs of abuse tested positive (one for cannabinoids, the other for opiates). It is possible that some of the clinical manifestations seen in this group were due to drugs other than ketamine.

In conclusion, ketamine abuse produces signs and symptoms similar to those caused by PCP but with a shorter duration of action. The complications after ketamine abuse appear to be relatively mild compared with those of other drugs of abuse. Treatment consists primarily of supportive care, benzodiazepines for sedation, and the prevention of rhabdomyolysis with i.v. fluid in agitated patients. Emergency physicians need to be aware of this emerging drug of abuse and be ready to manage the potential complications that may be encountered when ketamine abusers present to the emergency department.

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