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TOXICOLOGY OBSERVATION

Altered Mental Status and End Organ Damage Associated with the use of Gacyclidine: A Case Series

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Abstract
Introduction Over the past decade, there has been a sharp increase in the number of newly identified synthetic drugs. These new drugs are often derivatives of previously abused substances but have unpredictable toxicity. One of these drugs is gacyclidine, a derivative of phencyclidine (PCP). Gacyclidine has been studied as a neuroprotective agent in trauma and as a therapy of soman toxicity. There are no previous reports of its use as a drug of abuse.
Case Reports During a two-month period in the summer of 2013, a series of patients with severe agitation and end-organ injury were identified in an urban academic Emergency Department (ED). A urine drug of abuse screen was performed on all patients, and serum samples were sent for comprehensive toxicology analysis. A total of five patients were identified as having agitation, rhabdomyolysis, and elevated troponin (Table 1). Three of the five patients reported use of methamphetamine, and all five patients had urine drug screens positive for amphetamine. Comprehensive serum analysis identified methamphetamine in three cases, cocaine metabolites in one case, and a potential untargeted match for gacyclidine in all five cases. No other drugs of abuse were identified.
Discussion This is the first series of cases describing possible gacyclidine intoxication. The possible source of the gacyclidine is unknown but it may have been an adulterant in methamphetamine as all patients who were questioned reported methamphetamine use. These cases highlight the importance of screening for new drugs of abuse when patients present with atypical or severe symptoms. Gacyclidine has the potential to become a drug of abuse both by itself and in conjunction with other agents and toxicity from gacyclidine can be severe. It is the role of the medical toxicology field to identify new agents such as gacyclidine early and to attempt to educate the community on the dangers of these new drugs of abuse.

Keywords Gacyclidine · Dissociative toxicity · Phencyclidine derivative

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Introduction

The past decade has seen an explosion in new synthetic drugs. In 2012, a total of 73 new psychoactive drugs were described by European authorities [1]. Many of these new chemical compounds are synthetic derivatives of currently illegal drugs. These new compounds can pose significant risks, which in some cases are greater than those of the original drug. To address this problem, the United States (US) Congress passed Senate Bill 3190 in 2012. This amendment to the Controlled Substances Act banned synthetic analogs of already controlled substances [2]. In spite of these efforts, many psychoactive substances are still readily available on the internet and in

local head shops where they face little regulation or quality control.

One psychoactive drug that has been the subject of extensive investigation is phencyclidine (PCP). First discovered in 1926, it was briefly used as an anesthetic but was quickly abandoned due to unwanted side effects including dysphoria and psychosis [3, 4]. PCP is a non-competitive inhibitor at the *N*-Methyl-D-Aspartate (NMDA) receptor in the central nervous system [5, 6]. Due to its dissociative effects, it gained popularity as a drug of abuse in the 1970's and was subsequently banned by the US Food and Drug Administration as a schedule 1 drug under the Controlled Substances Act [6]. Since that time, the use of another NMDA antagonist, ketamine, has been widely accepted by the medical community for use as a dissociative anesthetic during painful procedures [7]. However, its relative availability has also lead to its illicit use.

Due to the beneficial medicinal properties of medications like ketamine, research into the effects of the NMDA receptor has continued. One compound identified in this research is gacyclidine ([cis(pip/me)-1-[1-(2-thienyl)-2-methylcyclohexyl]piperidine])(Fig. 1) which is also an antagonist at the NMDA receptor [8, 9]. Gacyclidine can be derived from tenocyclidine (TCP) [10], and has a binding affinity eight times greater than PCP at the NMDA receptor [11, 12]. Given its potency, there is concern that it could become a drug of abuse. It was initially studied for its potential neuroprotective effects after spinal cord and brain injuries [13–17] and after organophosphate poisoning [18, 19]. No human studies have specifically investigated gacyclidine intoxication.

With limited data on gacyclidine, human toxicity is not well described. We present a case series of patients who exhibited severe agitation and multi-organ dysfunction, who all were seen at our emergency department (ED) over the course of 2 months. Each patient ED staff was able to talk to report the use of methamphetamine, yet the severity of their presentation raised our suspicion for alternative or additional substances. Subsequent untargeted toxicologic analysis identified gacyclidine as a potential compound match in samples from all five patients.

Case Series

Over a 2-month period in the summer of 2013, a series of patients presented to a single urban academic ED with severe agitation and end-organ dysfunction not typically seen with commonly used drugs of abuse in this region. Due to concerns about the presence of an adulterant, or the emergence of a new drug of abuse in the community, serum samples were sent for comprehensive toxicology analysis.

All patients had urine samples tested for amphetamines, barbiturates, benzodiazepines, cocaine metabolites, and opiates. Samples were run on a Beckman Coulter automated enzyme immunoassay. Serum samples were sent to the clinical and environmental toxicology laboratory at the University of California, San Francisco (UCSF). Initial targeted analysis using liquid chromatography time-of-flight mass spectrometry was performed, and the results were compared to a library of 214 drugs of abuse including 19 synthetic cathinones and 33 synthetic cannabinoids. Positive results were compared to a known reference sample. In addition, untargeted time-of-flight mass spectrometry was performed. Peaks seen on this analysis were compared to a library of 9,020 compounds with mass matches flagged as potential positive results.

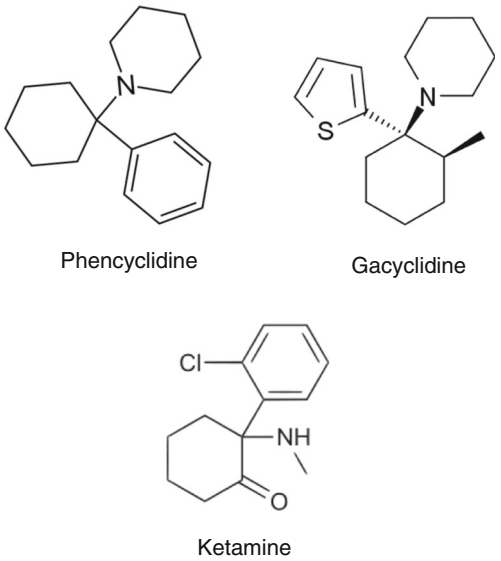

Fig. 1 Structural similarities of non-competitive NMDA antagonists

Case One

A 27-year-old man with no known past medical history was brought to the ED by police after being found confused and combative, breaking into cars in his neighborhood. On presentation, he was agitated and attempted to bite hospital staff and police officers and was placed in a spit mask. He was tachycardic, hypertensive, tachypneic (40 breaths per minute), and hyperthermic (39.2 °C). He was intubated due to the severity of his agitated delirium and concern for his safety. Initial laboratory analysis was significant for acute kidney injury, rhabdomyolysis, and elevated troponin as summarized in Table 1. His electrocardiogram (ECG) showed sinus tachycardia without ischemic changes. Imaging revealed bilateral pneumothoraces, pneumomediastinum, and pneumopericardium. He was also noted to have two rib fractures and extensive subcutaneous emphysema. He underwent a tube thoracostomy shortly after admission. Over the course of the next 4 days, he clinically improved, was extubated, and his chest tube was removed. On hospital day 4, the patient removed his own IV line and left the hospital against medical advice.

Table 1 Patient characteristics

Patient number	One	Two	Three	Four	Five
Age and gender	27-year-old male	49-year-old male	47-year-old male	47-year-old female	47-year-old male
Initial heart rate[a]	167	123	128	162	75
Initial blood pressure[b]	141/119	58/26	119/58	137/90	85/44
Initial temperature[c]	39.2	37.3	37.4	38.1	35.6
Peak creatinine kinase[d]	2,413	28,305	13,923	1,780	62,694
Peak serum creatinine[e]	1.84	2.07	3.84	1.47	5.9
Peak troponin I[f]	0.08	8.07	0.21	0.40	not done
Intubation	Yes	Yes	No	No	Yes
Dialysis	No	No	No	No	Yes
ICU[g] admission	Yes	Yes	Yes	No	Yes
Hospital length of stay	4 days	6 days	69 days	12 h	66 days

[a] Beats per minute

[b] mmHg

[c] Degrees celsius

[d] units/l (normal range 0–250)

[e] mg/dL (normal range 0.44–1.27)

[f] ng/mL (normal range <0.04)

[g] Intensive care unit

Case Two

A 49-year-old man with no known past medical history was brought to the ED by ambulance after being found running through traffic. He was severely agitated when EMS arrived on scene, and during transport, he became unresponsive and was found to be in cardiac arrest. He was intubated during transport, and received several minutes of chest compressions and 2 mg of intravenous epinephrine. On arrival in the ED, he had regained pulses and was noted to be tachycardic and hypotensive with poor peripheral perfusion. Initial ECG showed no ischemic changes. Laboratory analysis revealed acute kidney injury, rhabdomyolysis, and elevated troponin (0.32 ng/mL on arrival) (Table 1). Initial imaging revealed no major traumatic injuries. Following admission, he developed worsening cerebral edema which was attributed to hypoxic brain injury. In spite of surgical intervention, the patient died on hospital day 6.

Case Three

A 47-year-old man was brought to the ED by ambulance after bystanders noted he was having difficulty ambulating. The patient had a reported history of methamphetamine abuse but stated he was otherwise healthy. On initial presentation, he was tachycardic and confused. Laboratory analysis revealed acute kidney injury with hyperkalemia (8.1 mEq/L), rhabdomyolysis, and elevated troponin (Table 1). His ECG showed sinus tachycardia with peaked T waves but no ischemic ST or T wave changes. He was treated with 4 l of 0.9 % saline solution along with insulin, dextrose, sodium bicarbonate, and continuous albuterol for his hyperkalemia. He was admitted to the intensive care unit (ICU) where his laboratory values rapidly improved. He remained altered and an MRI showed symmetric white matter changes in the anterior centrum semiovale and corticospinal tracts. The patient remained in the hospital for 2 months, after which he was transferred to a skilled nursing facility due to persistent inattention and delirium.

Case Four

A 47-year-old woman with a history of hepatitis C was brought to the ED by ambulance after being found down next to a bus stop. On presentation, she was noted to be agitated and confused, stating that she had drunk “juice” someone had given her. She was tachycardic, hypertensive, tachypneic (32 breaths per minute), and hyperthermic. Her ECG showed sinus tachycardia with left axis deviation and Q waves in leads II, III, and AVF. Initial laboratory analysis revealed acute kidney injury, rhabdomyolysis, elevated troponin, and a lactic acidosis (Table 1). She was treated with midazolam and 4 l of 0.9 % saline solution. Over the course of the next 12 h, she returned to her baseline mental status, at which point she left the hospital against medical advice.

Case Five

A second 47-year-old man was brought to the ED by private vehicle after being found down next to a gas station. He had a

Table 2 Toxicologic analysis results

Patient number	One	Two	Three	Four	Five
Urine drug screen results	Amphetamine	Amphetamine	Amphetamine	Amphetamine	Amphetamine Opiates
Targeted serum analysis[a] (concentration in ng/mL)	Methamphetamine (452) Ecgonine Methyl Ester (55)	Methamphetamine (654) Caffeine (2435) Amphetamine (235)	Methamphetamine (245)	Caffeine (1545)	Acetaminophen (525)
Untargeted Serum Analysis[a]	Gacyclidine	Gacyclidine	Gacyclidine	Gacyclidine	Gacyclidine

[a] Liquid chromatography time-of-flight mass spectrometry performed on Agilent LC1200- TOF6230

history of methamphetamine and ethanol abuse and had reportedly been using that day. On arrival, the patient was noted to be hypotensive with decreased mental status and required intubation for airway protection. Initial ECG showed sinus tachycardia without ischemic changes. Laboratory evaluation was significant for a lactic acidosis (lactate 3.7 mEq/L), acute kidney injury, and rhabdomyolysis (Table 1). This patient had a prolonged hospital course with slow improvement in his mental status and persistent renal failure requiring dialysis. He was eventually discharged after 2 months in the hospital. He underwent a brief course of outpatient dialysis but has since fully recovered his kidney function.

Toxicologic Screening Results

Urine drug screens were performed on all five patients, and all tests returned positive for amphetamines. Targeted and untargeted serum analysis was also positive for methamphetamine in three of five patients. In all five serum samples, gacyclidine was identified as a potential compound match from untargeted analysis. The full positive results of both serum and urine testing are outlined in Table 2. References ranges for the substances detected are outlined in Table 3.

Discussion

This is a case series of five patients who tested positive for amphetamine on urine drugs screens and gacyclidine in untargeted serum analysis over a 2-month period. Patients presented with profound mental status changes beyond what is normally seen with illicit drug use in this community. These patients also exhibited consistent findings of acute kidney injury, rhabdomyolysis, and in some cases elevated troponin.

Gacyclidine was first synthesized from PCP in 1982 [11]. Due to its action as a potent non-competitive NMDA antagonist, gacyclidine has been studied for its neuroprotective effects in spinal cord and brain trauma [8, 13, 14, 16, 17]. One particularly attractive characteristic is its decreased neurotoxicity when compared to other NMDA receptor antagonists [20–22]. Initial animal research in these areas was promising, but early human studies have not shown improved outcomes [14–16]. Current research is being conducted to evaluate the utility of its local application in the middle ear to treat severe tinnitus [23]. Gacyclidine has also been studied as a neuroprotectant in organophosphate poisoning, primarily focusing on the chemical warfare agent soman [18, 19]. To date, research has not focused on the pharmacodynamics of gacyclidine and the human effects of intoxication have not been previously reported. There are some structural similarities between gacyclidine and other non-competitive NMDA antagonists, which suggest similar pharmacologic activity (Fig. 1). Previous experience with other non-competitive NMDA receptor antagonists such as PCP and ketamine indicates that severe intoxication would have prominent sympathomimetic and dissociative characteristics [5, 6]. As research progresses to include other possible uses of this medication, further elucidation of the effects specific to gacyclidine may occur.

Table 3 Reference ranges for detected substances

Drug	Serum therapeutic/ recreational concentration (ng/mL)	Serum toxic concentration (ng/mL)	Serum lethal concentration (ng/mL)
Acetaminophen	10,000–25,000	100,000–150,000	>200,000–300,000
Caffeine	4,000–10,000	15,000–20,000	>80,000–180,000
Methamphetamine	0–100	150	>1,000–18,000
Amphetamine	20–100	200	>500–1000

Source: Schulz M, Iwersen-Bergmann S, Andresen H, and Schmoldt A (2012) Therapeutic and toxic blood concentrations of nearly 1,000 drugs and other xenobiotics. Crit Care 16(4): R136

This series of patients had a consistent clinical presentation and serum toxicologic analysis that suggests the presence of gacyclidine. The detection of a substance, however, does not prove intoxication. Alternative causes of our patients' presentation must also be considered. Many different agents have been reported to cause agitated delirium including methamphetamine, cocaine, and synthetic cathinones [24]. Altered mental status with multi-organ dysfunction can also result from infection, neuroleptic malignant syndrome, and heat stroke. The presentation of agitated delirium does not necessitate an alternative cause beyond common substances of abuse. It was, instead, the severity of the presentation combined with the number of patients seen in a short time which lead us to perform more extensive toxicologic analysis. We specifically chose the lab at UCSF for its ability to do targeted analysis for many of the emerging drugs of abuse including synthetic cathinones and synthetic cannabinoids.

It is important to understand the limitations of the detection techniques used in these cases. Most toxicology labs which perform "comprehensive" drug screens use a targeted approach. This involves performing GC/MS or liquid chromatography/mass spectrometry and comparing the peaks against a known library of substances. These positive results are then confirmed using a reference standard of known concentration. This can definitively identify the presence of a substance and often can allow for the calculation of a concentration. This technique ignores peaks which are not part of the detection library. Some specialized labs are able to perform what is called untargeted analysis. In these cases, peaks are compared to a library of known substances and their expected peaks on mass spectrometry. Positive results obtained through this method cannot be verified if no reference sample can be obtained. This approach allows for the early identification of new drugs of abuse, however that ability comes at the price of uncertainty.

Caution must be used when attempting to fully implicate gacyclidine in these cases. First, due to the lack of a reference sample, we were unable to definitively confirm the initial mass spectrometry findings. Second, the discovery of a substance in a biologic sample does not prove it is the cause of intoxication. Finally, there are more common substances which are known to cause excited delirium. It is impossible to know if gacyclidine was the cause of, or contributed to, the severity of each patient's presentation. However, the consistent clinical picture combined with the consistent match of gacyclidine in the patients' serum suggests that it may have played a role.

As more synthetic drugs of abuse are developed, a critical role of toxicologists will be to recognize and characterize the adverse effects associated with them. Collaboration with large toxicology labs, such as the one at UCSF, is vital in this endeavor. However, this is just the first step. Educating fellow clinicians and the community as a whole is of utmost importance. Knowledge of the risks associated with the use of these new drugs will empower the community to combat their use.

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Conflict of Interest No conflicts to declare.

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