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Ketamine in Non-Hospital and Hospital Deaths in New York City

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ABSTRACT: We reviewed all ketamine-positive deaths (87) examined at the New York City Office of Chief Medical Examiner over a two-year period (1997 to 1999). There were 15 non-hospital deaths with 12 due to acute multidrug intoxications, one due to sarcoidosis, and two due to physical injury (blunt and thermal). In no instance was a fatal intoxication caused exclusively by ketamine. Opiates (10/15), followed by amphetamines (7/15) and cocaine (6/15), were the most frequent co-intoxicants. Ethanol was found in only one death. The race of all decedents was white and the majority were men (11/15) between the ages of 18 and 30 years. The remaining 72 instances of positive ketamine findings were hospital deaths following surgical procedures or burns.

KEYWORDS: forensic science, forensic pathology, forensic toxicology, ketamine, illicit drug abuse, fatality

Ketamine is a parenterally administered anesthetic induction agent used since 1972. It combines sedative, anesthetic, amnestic, and analgesic properties. It is used in pediatric, obstetric, cardiothoracic, veterinary, and trauma surgery for anesthesia and in burn patients for analgesia (1,2). Ketamine, an arylcyclohexylamine, is structurally related to phencyclidine (PCP) and can produce some of the same effects. These include auditory, visual, and sensory hallucinations, delirium, and so-called "dissociative anesthesia." Dissociative anesthesia has been described as a state of catalepsy in which the eyes remain open with a slow nystagmic gaze. Ketamine, like PCP, blocks the receptor for N-methyl-d-aspartate (NMDA), an excitatory amine in the human brain (3). Also, it is believed to affect opioid, noradrenaline, and serotonin receptors.

In the 1970s on the West Coast of the United States, ketamine ("Vitamin K," "Super K," "Special K") became a drug of abuse. Together with MDA (methylenedioxyamphetamine) and MDMA (methylenedioxymethamphetamine), ketamine has gained renewed popularity in the 1990s among the "club" scene and at "raves" (all night clandestine dances to loud repetitive synthesized music) (4,5). Ketamine can be made into a powder that can be taken intranasally or orally. Currently in New York City, 100 mg of ketamine is sold for approximately $45. The illicit popularity of the drug is due to its induction of a "separate reality," "near death/lack of fear of death," or "out of body" experience.

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The psychological effects of ketamine depend upon the dosage and routes of administration which include nasal, oral, intramuscular, and intravenous. The effects are brief (about 30 min) and are produced by smaller doses (e.g., 50 mg intravenously) than those used for anesthesia (typically 2 to 10 mg/kg). Ketamine is metabolized in the liver by the cytochrome P-450 enzymes to norketamine (by N-demethylation) which may undergo dehydrogenation to dehydronorketamine. Norketamine has one third of the activity of ketamine and can be hydroxylated and conjugated to water-soluble substances that are excreted in the urine (2).

In this study, all ketamine-positive deaths examined at the New York City Office of Chief Medical Examiner over a two-year period were reviewed. We compare the postmortem ketamine results in subjects illicitly using ketamine with results from hospital deaths where ketamine was used as a therapeutic agent.

Materials and Methods

All instances in which ketamine was found by routine toxicological testing of autopsy samples at the New York City Office of Chief Medical Examiner (OCME) from January 1997 to January 1999 were identified through the toxicology laboratory database with subsequent review of the OCME autopsy files.

The Office of Chief Medical Examiner investigates all unexpected, violent, and suspicious deaths in New York City. Toxicological testing is performed routinely on all autopsies. In 1997 and 1998, the OCME performed 10 764 autopsies.

The conclusion that death was caused by an acute intoxication requires that the toxicology results be within the range typically encountered in such fatalities, that the history and circumstances be consistent with a fatal intoxication, and that the autopsy fails to disclose a disease or physical injury that has an extent or severity inconsistent with continued life. In deaths caused by drug intoxication with more than one drug in concentrations greater than trace amounts, it is customary to include all of the identified drugs in the cause of death.

Autopsy blood specimens were collected with addition of sodium fluoride and stored at 4°C. The toxicologic laboratory at the Office of Chief Medical Examiner analyzed all specimens. Routine initial toxicologic testing, using gas chromatography with a nitrogen phosphorous detector (GC/NPD), included detection of ketamine. All initial positive findings were confirmed by gas chromatography/mass spectrometry (GC/MS). Ketamine was quantified (limit of quantitation: 0.1 mg/L) by GC/NPD.

Total opiates were determined by radioimmunoassay (blood) or by enzyme immunoassay (urine). Results were considered positive by radioimmunoassay if opiates were detected in the blood at concentrations equal or greater than 0.1 mg/L. Results were considered positive by enzyme immunoassay if opiates were detected in

urine at concentrations equal to or greater than 0.3 mg/L. All samples considered positive by radioimmunoassay were, in addition, analyzed by gas chromatography/mass spectrometry (GC/MS) for free morphine and by GC/NPD for codeine, hydrocodone, and oxycodone.

Results

Non-Hospital Deaths (Total = 15)

Ketamine was identified in samples from 87 medical examiner autopsies in New York City. Of those, 15 were non-hospital deaths (Table 1). No fatality was caused exclusively by ketamine. Opiates were detected in ten acute intoxication deaths (all were pronounced dead at the scene). The remaining five deaths included: two acute multidrug intoxications (one with intracerebral hemorrhage and one with hyperthermia), one sarcoidosis of the heart, and two physical injuries. The traumatic deaths included a fall from height and a burn victim.

Opiates (10/15), followed by amphetamines (7/15) and cocaine (6/15), were the most frequent co-intoxicants. Ethanol was found in only one death. The race of all decedents was white and the majority were men between 18 and 30 years of age. The circumstances of the five deaths in which opiates were *not* detected, are described.

1. Intracerebral Hemorrhage

A 22-year-old man was found on the floor of his locked apartment by a roommate. He was last seen the night before at a party. In the room were drug pipes and brown vials. There was no attempted resuscitation and he was pronounced dead at the scene. He had an acute, large, left frontal lobe cerebral hemorrhage. Amphetamine, methamphetamine, benzoylecognine (BE), and ketamine were detected in the blood. At autopsy, there was no evidence of underlying hypertensive cardiovascular disease. The proximate cause of death was acute multidrug intoxication.

2. Sarcoidosis

A 41-year-old man was witnessed to collapse the morning following a party. The decedent was brought to the hospital and pronounced dead on arrival without therapeutic intervention. At autopsy, the right and left ventricles including the septum of the heart were replaced by a firm white infiltrating mass. Microscopic examination revealed fibrosis, non-caseating granulomas, and multinucleated giant cells. Silver and acid fast stains were negative for microorganisms. There was slight granulomatous involvement of the lung. Ketamine, MDA, and MDMA were detected in the blood. The proximate cause of death was sarcoidosis with the acute intoxication as a contributing condition.

3. Thermal Injuries from Residential Fire

An 18-year-old woman was found on fire in her bedroom by a female roommate. She had a history of ketamine abuse and cigarette smoking. She was pronounced dead at the scene. At autopsy, she had thermal injuries with charring of 95% body surface area with inhalational injury and soot in the trachea. Her carboxyhemoglobin was 12%. Ketamine was detected in her blood and urine. The fire was ruled accidental due to heat from smoking material. The deceased was an art student and had paint supplies in her room.

4. Blunt Injuries from Fall from Height

A 28-year-old man was found in the back of a nightclub to which he had earlier gained admission and checked his coat. His body was found in the early morning by an employee who went outside on break. Access to this area was restricted to employees. There was open access to the 7-story roof above the decedent. Two vials of white powder were found on his person and white powder was visible in his nostrils. At autopsy, there were rib fractures with lung contusions and hemothorax, pelvic fractures, and lacerations of the spleen and kidneys. There was peritoneal, retroperitoneal, and subdural hemorrhage. The decedent was brought to the hospital and

TABLE 1—*Postmortem findings including toxicology results in non-hospital, ketamine-positive deaths.*

	Age/Race/Sex	Cause of Death [Anatomic Finding]	Ketamine (mg/L)	Blood Opiates (mg/L) [Free Morphine mg/L]	Additional Blood Toxicology Findings (mg/L)
1	22 WM	Acute intoxication [intracerebral bleed]	Detected*	0	BE 0.3, Amphetamine 0.2, Methamphetamine 1.6
2	41 WM	Cardiac sarcoid with acute intoxication	<0.1	0	MDA 0.1, MDMA 0.5
3	18 WF	Thermal injuries	2.1	0	
4	28 WM	Blunt injuries	1.0	0	MDA <0.1, MDMA 1.3
5	18 WM	Acute intoxication [hyperthermia]	0.2	0	MDA <0.1, MDMA 1.7, Cannabinoids
6	20 WM	Acute intoxication	1.1	0.5 [0.2]	Cocaine <0.1, Methamphetamine <0.1, BE <0.1
7	25 WM	Acute intoxication	<0.1	0.3 [<0.1]	
8	42 WM	Acute intoxication	0.2	0.2 [<0.1]	ETOH 0.02†, Cocaine 0.2, Methamphetamine 0.1, BE 2.0
9	21 WM	Acute intoxication	<0.1	0.3 [detected‡]	Diazepam 0.2
10	20 WF	Acute intoxication	Detected*	0.6 [detected‡]	Cocaine <0.1, MDA 0.1, MDMA 0.3, BE 1.6
11	19 WF	Acute intoxication	Detected*	0.7 [0.2]	
12	22 WF	Acute intoxication	Detected*	0.3 [<0.1]	BE 0.2, Cannabinoids, Fluoxetine 0.4, Trazodone 0.9
13	20 WM	Acute intoxication	Detected‡	1.0 [0.3]	PCP 0.01
14	33 WM	Acute intoxication	Detected‡	0.2 [<0.1]	Cocaine <0.1, Diazepam 0.5, Fluoxetine <0.1, BE 4.2
15	23 WM	Acute intoxication	Detected‡	0.5 [0.2]	

* Ketamine detected in blood (GC/NPD and GC/MS); quantitation not performed.
† Ethanol [ETOH g%].
‡ Detected in urine; quantitation not performed.

pronounced dead on arrival without therapeutic intervention. Ketamine, MDA, and MDMA were detected in his blood.

5. Hyperthermia

An 18-year-old man collapsed and had seizures outside a dance club. Resuscitation was attempted at the scene. The postmortem rectal temperature, measured 2½ after the collapse, was 103°F (39.4°C). At autopsy there was no gross or microscopic disease. Ketamine, MDA, and MDMA were detected in the blood. The vitreous chemistries included a creatinine of 0.7 mg/dL and urea nitrogen of 10 mg/dL. The proximate cause of death was acute multidrug intoxication.

Hospital Deaths (Total = 72)

The remaining 72 decedents had been treated and pronounced dead in hospitals. Postmortem ketamine concentrations were determined in 31 of the decedents (Table 2). The majority of ketamine positive hospital fatalities were acute traumatic deaths (54/72) that had emergent surgery. The remainder were burn unit and pediatric/obstetric surgical deaths. Therapeutic ketamine administration was confirmed or supported by hospital records and/or clinical history. Table 3 shows the ketamine blood concentrations by specimen site (heart, peripheral vessel, cavity, or undesignated).

TABLE 2—*Postmortem ketamine concentrations (mg/L or mg/Kg) in hospital vs. non-hospital deaths.*

	Hospital Deaths		Non-Hospital Deaths	
Specimen	*n*	Range (mean)	*n*	Range (mean)
Blood	31	<0.1–4.3 (0.9)*	8	<0.1–2.1 (0.9)
Brain	4	0.4–7.2 (2.9)†	1	<0.1
Liver	2	0.4–3.2 (1.8)‡	0	…

NOTE—Results with concentrations of less than 0.1 were excluded from the mean calculation: hospital deaths [blood: 5] and non-hospital deaths [blood: 3].

* Includes a patient in the burn unit for several weeks (4.3 mg/L).

† Includes a patient witnessed to jump from a height of five stories while hospitalized for depression with subsequent emergent surgery [3.6 mg/L (blood) and 7.2 mg/kg (brain)].

‡ Includes an asthmatic patient given 2 mg/kg of intravenous ketamine at 6:30 a.m. and who died at 8:10 a.m. Ketamine concentration in the blood was 2.8 mg/L and in the liver was 3.2 mg/kg.

TABLE 3—*Postmortem ketamine blood concentrations (mg/L) in hospital vs. non-hospital deaths by specimen collection site.*

	Hospital Deaths		Non-Hospital Deaths	
Site*	*n*	Range (mean)	*n*	Range (mean)
Heart	10	<0.1–4.3 (0.93)	3	<0.1–2.1 (2.1)
Peripheral	5	0.1–2.8 (0.94)	2	0.1–1.1 (0.6)
Cavity	9	0.1–1.2 (0.58)		…
Undesignated	7	<0.1–3.6 (1.1)	3	<0.1–1.0 (0.4)

NOTE—Results with concentrations of less than 0.1 mg/L were excluded from the mean calculation: hospital deaths [heart: 2, cavity: 1, undesignated: 2] and non-hospital deaths [heart: 2, undesignated: 1].

* One hospital death had a ketamine concentration of 0.6 in both heart and subclavian blood specimens.

Discussion

In keeping with its known wide therapeutic margin, there were no deaths due exclusively to ketamine intoxication over a two-year period in New York City. In ten of the non-hospital deaths, blood samples contained opiates and autopsies failed to disclose a lethal disease or physical injury. Methamphetamine, substituted amphetamines, and cocaine were also common co-intoxicants. As in any multidrug intoxication, the complex interactions that may occur cannot be completely delineated. Ketamine is a respiratory depressant similar to opiates (6) and also has centrally mediated sympathomimetic cardiovascular effects.

The consistent presence of opiates in these fatalities with the absence of any sole ketamine intoxication deaths, suggests that opiates play a dominant role in the fatalities. The typical mechanism of death due to acute opiate intoxication is respiratory depression. Since ketamine also causes respiratory depression, its contribution to these deaths is likely.

Heroin is adultered with many substances either to dilute ("cut") the drug or for added effects. Addition of ketamine could be part of a designer mix. The strict epidemiological profile of the decedents, however, tends to favor an intentional seeking of ketamine. If ketamine is a common heroin adulterant in New York City, we would expect to see a broader epidemiological profile of acute intoxication deaths with opiates and ketamine.

Four of the remaining five non-hospital deaths (no opiates detected), had a demonstrable immediate cause of death, lethal disease, or physical injury. These included: an intracerebral hemorrhage, sarcoidosis, burns, and blunt injury. The fatality with the intracerebral hemorrhage (case #1) had benzoylecgonine, methamphetamine, amphetamine, and ketamine detected in the autopsy blood. Intracerebral hemorrhage due to cocaine and/or amphetamines in non-hypertensive patients is well described (7–9). Experimentally, ketamine injected directly into the cerebral circulation results in a sudden increase in blood pressure and heart rate (10,11). These hypertensive effects are cited as one of the benefits of using ketamine as an anesthetic. Most anesthetics have cardiac depressive side effects, and therefore ketamine is uniquely suited for trauma and pediatric surgery where hypotension is a major concern. Since ketamine increases blood pressure, it was included along with cocaine and amphetamines as the underlying cause of the intracerebral hemorrhage.

The mechanism of death in the sarcoidosis fatality was an arrhythmia (case #2). In the absence of any toxicologic findings, the death would be certified solely due to sarcoidosis. The presence of an acute intoxication complicates the determination of the cause of death. Since it is physiologically plausible that ketamine and/or substituted amphetamines contributed to the arrhythmia, the drugs were included as a contributory condition.

Ketamine was found in two deaths (case #3 and #4) from physical injury (one blunt and one thermal). One may postulate that ketamine-induced perceptual distortions produced the perilous circumstances surrounding these two deaths; however, in both instances there was physical injury inconsistent with life. Cocaine has been demonstrated in a substantial proportion of all violent deaths in New York City (12). The neurobehavioral effects of cocaine, as well as ketamine, may increase the likelihood that a user will receive violent fatal injuries. We invoke acute intoxications in deaths either when it plays a physiologic role in causing the death or when the circumstances do not make sense without it (e.g., drowning in a bathtub). The proximate causes of death in these two fatalities are the injuries.

Similar to other hallucinogens, ketamine could put users at risk for trauma. Although ketamine is similar to PCP, it appears not to have some of the antisocial, violent side effects. In addition, its concurrent use with opiates may temper aggressive behavior. Aside from a possible predisposition to violent deaths or polysubstance abuse, ketamine by itself appears to carry a low mortality.

In the one remaining non-hospital death (case #5), ketamine and substituted amphetamines were detected in the blood and hyperthermia was noted during the scene investigation. Substituted amphetamines also are a popular drug of abuse of the "club/rave" culture and have amphetamine and hallucinogenic properties. These drugs include MDA and MDMA which are commonly referred to as XTC, Adam, and the love drug (4). Thus it is not surprising to find them in 7 of the 15 non-hospital deaths. Sudden death and hyperthermia have been described with the use of substituted amphetamines (9,13). Hyperthermia may be a simple manifestation of the intoxication or may be the immediate cause of death. One case of malignant hyperthermia has been reported following ketamine anesthesia for a muscle biopsy in a child (2).

Three other interesting findings deserve comment. First, the race of all of the non-hospital deaths was white and the majority were men and between 18 and 30 years of age. Second, ethanol (a trace amount which may be due to postmortem production) was found in only one death. These findings may be a reflection of the "club/rave" culture in New York City. Third, diazepam was found in two deaths. Benzodiazepines are used clinically as an adjunctive agent to attenuate some of the unpleasant psychic effects of ketamine (1). Since ketamine abuse by medical professionals has been described (14), it raises the question of whether this combination is purely coincidental.

The hospital fatalities provide postmortem ranges of various tissue concentrations following the therapeutic use of ketamine. Although abusers typically take lower doses than used in anesthesia, the postmortem drug concentrations in the two groups (Table 2) are similar. This may be due to the low therapeutic margin of ketamine, which is also consistent with the absence of any sole ketamine intoxication deaths. The variable length of time of survival in the hospital after ketamine therapeutic administration and its short half-life may also account for this finding. Other reports of fatal ketamine overdoses describe blood concentrations of 1.8 to 27.4 mg/L while blood concentrations sufficient to provide surgical anesthesia have been given to range from 1.0 to 6.3 mg/L (15). The blood concentrations from various sample sites (heart, peripheral, etc.) are similar (Table 3) and show no variation indicative of postmortem redistribution (16).

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