

CASE REPORT

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A Fatal Chronic Ketamine Poisoning

ABSTRACT: A few papers in the literature reported incident deaths by acute ketamine poisoning. In this paper, we report an unusual homicide caused by chronic ketamine poisoning. The victim was a 34-year old married woman with no previous medical history (except as reported herein) who died in her own home. The court investigation revealed that she was chronically poisoned by her husband over a period of about one year in an act of homicide. Determination of ketamine concentrations in autopsy specimens was carried out with gas-chromatography/mass spectrometry (GC-MS). The results showed that ketamine concentration was 21 µg/mL in gastric contents, 3.8 µg/mL in blood and 1.2 µg/mL in urine. The most striking forensic findings were cardiac muscle fibrosis and hyaline degeneration of small arteries in victim's heart, the pathological features of ketamine poisoning previously reported only in animal studies.

KEYWORDS: forensic science, poisoning, homicide, cardiac fibrosis, ketamine

Ketamine is a non-barbiturate anaesthetic providing good analgesia with only moderate amnestic and hypnotic effects. Ketamine at low anaesthetic dosages produces a trance-like state, called "dissociative anaesthesia" with alterations in mood, cognition and body image, which causes patients to feel detached from their immediate surroundings without inducing drowsiness (1). There are only a few papers in the literature reporting incident deaths by acute ketamine poisoning (2,3). Here we report a homicide caused by chronic poisoning using ketamine perpetrated by the victim's husband.

Determination of ketamine concentrations in autopsy specimens was carried out with gas-chromatography/mass spectrometry (GC-MS). The results showed that ketamine concentration was 21 µg/mL in gastric contents, 3.8 µg/mL in blood and 1.2 µg/mL in urine. Reported LD50 is 224 ± 4 mg/kg in mice and 229 ± 5 mg in rats. The administered doses of ketamine in this case were 100–300 mg, well below LD50, thus ruling out the possibility of acute poisoning. However, the most striking forensic findings were cardiac muscle fibrosis and hyaline degeneration of the small arteries of the victim's heart, which are pathological features of ketamine poison previously reported only in animal studies (4). This led us to consider the possibility of chronic poisoning with ketamine, which the police and Court investigations eventually established to be the case.

Circumstances

The deceased was a 34-year old female who resided in an apartment with her husband. The husband stated that she was discovered unconscious with no respiration or heart beat shortly after bathing and then drinking a cup of coffee prepared by him. She was trans-

ported by ambulance to the emergency room of a local hospital and pronounced dead.

Reconnaissance Investigation

The scene was protected and inspected over the following days. During inspection, a coffee cup was collected and ketamine injections (100 mg vials) were found in the refrigerator. Reconnaissance investigation was carried out and autopsy and toxicological analyses were performed. The following information was revealed through investigation:

1. The victim was in good general health with no previous medical history until some time in 2002, when the victim experienced headache and insomnia. In September 2002, she was found unconscious with suddenly arrested respiration and heartbeat, which symptoms recurred on three or four subsequent occasions. However, medical examinations, including ECG, on each of these occasions failed to find evidence of illness in the vital organs.
2. The husband had married the victim, not for love, but only because he wanted to become a postgraduate student of her father. Some three years before the reported incident, the husband had fallen in love with another young girl.
3. The husband was a paediatric surgeon who had easy access to ketamine and knowledge of its toxicity.
4. Approximately a year before her death, the husband began preparing a cup of tea or coffee for his wife after her bath. This was something he had never done before.
5. The husband's fingerprints were found on the surface of empty ketamine glass vials from which were collected from the garbage can, as well as on the coffee cup used by his wife shortly before she collapsed.

After receipt of the initial autopsy report, the police decided to detain the husband and investigate him as a suspect. Finally, the husband confessed that he had been using ketamine to poison his

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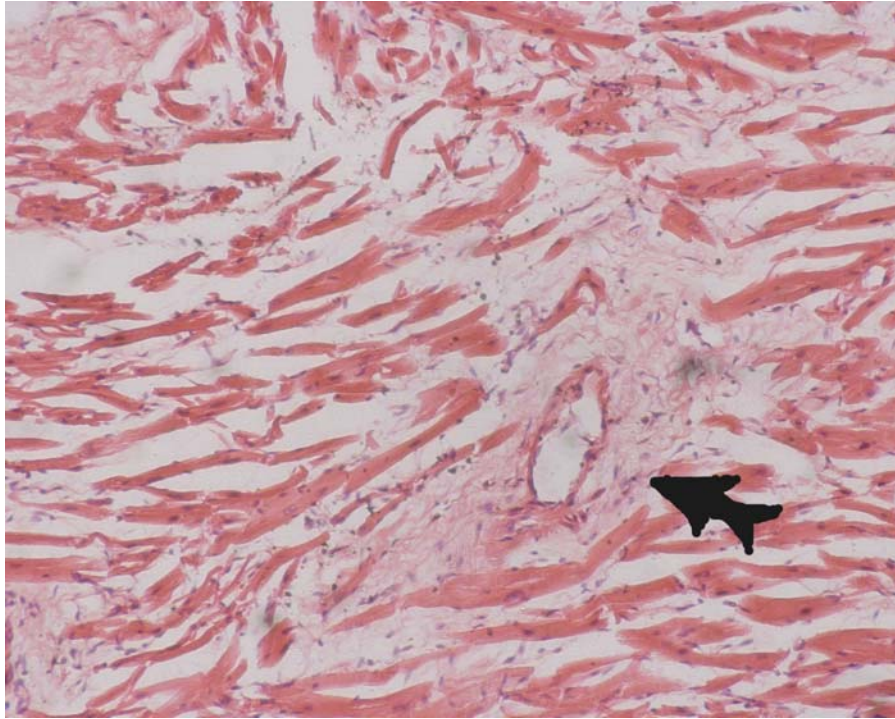


FIG. 1—Showing extensive cardiac fibrosis around the small artery that was hyaline degenerated (as shown by arrow).

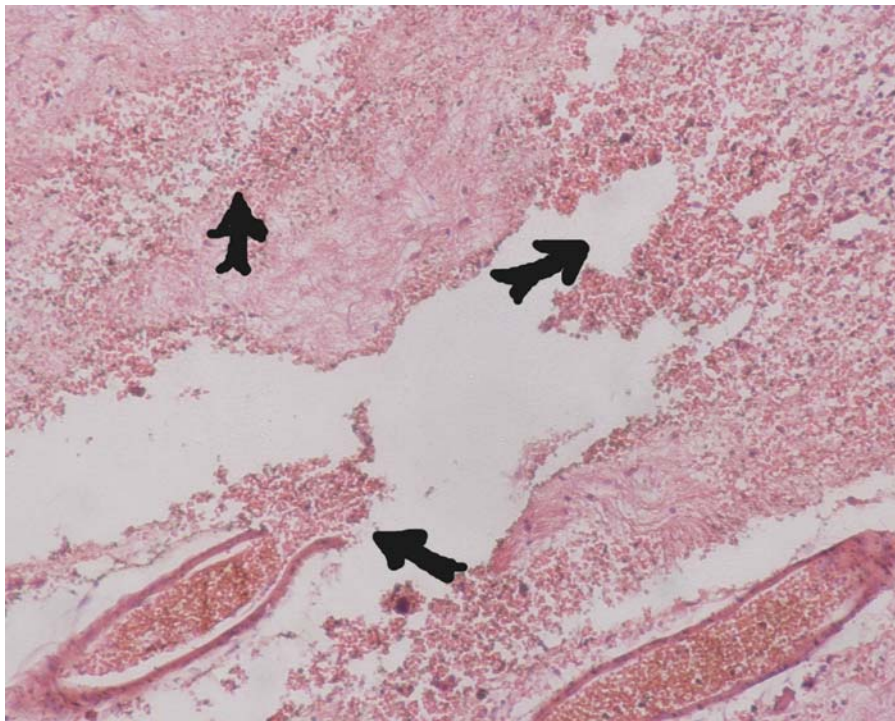


FIG. 2—Showing disruption of small veins and haemorrhage in the brain tissue (as shown by arrows).

wife since September 2002, because the lover wanted to marry him, but he did not want to lose assets in a divorce settlement. At first, he added one vial (100 mg) of ketamine to his wife's coffee cup. After four or five such additions, he found no noticeable symptoms of toxicity. He then added two vials (200 mg) to her drink. The victim began to show some symptoms of ketamine toxicity. Each time such intoxication occurred, the husband informed the victim's fam-

ily and sent her to hospital for clinical examination. At the hospital he stated that he had found his wife with arrested respiration and pulse. No unambiguous diagnosis was made, but hospital doctors suspected unusual cardiac malfunction. The victim's family members accepted the doctors' conclusion and believed that the husband was taking good care of his wife. Finally, the husband added three vials (300 mg) of ketamine to the coffee and the death occurred.

Autopsy Findings

An autopsy was performed 20 h after death. Body weight at autopsy was 48 kg. No injuries existed on the surface or inner tissues of the corpse, in particular, no injury suggesting assault with strangulation or mechanical asphyxia. Lungs were oedematous and congested (right 775 g; left 700 g) and had haemorrhagic spots on the surface. The heart (220 g) had proportionate chambers and was otherwise unremarkable, but had leukoplakia and haemorrhagic spots on the surface. The thickness of the left heart wall was 1.3 cm and the right was 0.4 cm. All valves were a normal size and in good working condition. The surface of the kidneys (right 220 g; left 225 g) was smooth. The brain (1550 g) was congested with no trauma.

Microscopic examination of the lungs confirmed pulmonary congestion and oedema. There were some heart-failure cells in the interstitial and alveolar cavity filled with oedema liquid, cellulose and erythrocytes. Histology of the heart showed widespread scattered cardiac muscle fibrosis around the small arteries. The newly-occurred necrosis foci had some infiltrated inflammatory cells. The endometrium of the coronary artery was slightly thickened. The brain showed signs of chronic hypoxic changes, including glial and formation of starch bodies and some oedema characteristics. Some small arteries were ruptured in the area of the internal capsule and had haemorrhagic spots. The small arteries in heart and brain showed shedding of endothelium and hyaline degeneration of smooth muscle. No glassy degeneration was found in the renal glomerulus. Samples of heart blood, stomach contents and urine were collected at autopsy, and 50 mL of coffee coloured stomach contents.

Toxicological Examination

Drugs in blood, stomach contents and urine were determined with gas chromatography/mass spectrometry (GC-MS), which revealed the absence of the following drugs or poisons: phenothiazine, Valium, opium, cocaine, ethanol, Organo-phosphorus pesticides, diphacin, Fumerin and others. However, the concentration of ketamine in these collections was as follows: 3.8 µg/mL in cardiac blood, 21 µg/mL in stomach contents and 1.2 µg/mL in urine. Ketamine was also detected in the dregs of the coffee cup.

Discussion

The autopsy revealed cerebral oedema, over-inflation of lungs, pulmonary oedema accompanied by hyperaemia, inter-alveolar and interstitial haemorrhages. All these signs pointed to an asphyxial death as defined by Walsh et al. (5). But there was no evidence of mechanical asphyxia, or autoerotic asphyxia in this case. We found widespread fibrosis of cardiac muscle fiber around the small arteries and heart-failure cells in the lungs.

What caused these changes? The victim had no history of bouts of myocarditis, hypertension or cocaine abuse. Autopsy examinations also did not support any of the abovementioned possibilities. The presence of ketamine and cardiac fibrosis were the only positive results in our forensic examinations.

Ketamine is an anaesthetic with a stimulatory effect on the cardiovascular system, producing tachycardia, increasing blood pressure and myocardial oxygen consumption, and causing mild respiratory depression. Respiratory depression is enhanced by overdosing, or by rapid intravenous injection (6,7). Ketamine induces characteristic changes in breathing patterns, causing phases of deep, less frequent breaths with brief apneustic episodes, as well as phases of

sighing inspirations with high tidal volumes and an end-inspiratory plateau. The apneustic episodes are probably caused by hyperventilation (8). Perhaps all these respiratory effects may have caused the asphyxia phenomenon in this case. Both anoxemia and/or the misuse of ketamine could have caused the cerebral oedema.

Ketamine is seldom used on psychiatric patients because of its tendency to cause hallucinations and bizarre nightmares (8). Because of its hallucinogenic effects, ketamine became a drug of abuse at the end of the 1970s (9). In recreational settings, it is typically used in low anaesthetic dosages (50–120 mg, i.m.), which produces marked synesthesia and euphoria (10,11). The combined effects of ketamine in some aspects may be similar to the experience of sexual orgasm (12). In the case being reported, police and Court investigations excluded non-medical abuse and sexual use of ketamine.

Toxicological analysis of blood taken from the heart revealed a ketamine concentration of 3.8 µg/mL. At investigation, the husband confessed that 100–200 mg of ketamine was added to her drink on each occasion. The last time he added 300 mg of ketamine to the coffee, all well within the therapeutic range (1.0–6.0 µg/mL). We suggest that the actual concentration in the blood at the time of death in this case is because ketamine is metabolised with a short half-life through the hepatic cytochrome P450-dependent enzyme system, and is further conjugated to glucuronide derivatives, which subsequently undergo renal elimination (7). Ketamine's effect of increasing intracranial pressure makes this anaesthetic unsuitable for use in patients with neurosurgical intervention (5,6). Marini et al. have described myocardial fibrosis in rabbits after chronic exposure under anaesthesia dosage to ketamine (4).

In this report, we suggest that the widespread myocardial fibrosis and hyaline degeneration of the small arteries was caused by large doses of ketamine; i.e., chronic ketamine poisoning. The husband's confession of systematically administering non-lethal doses to the victim is consistent with our observations at post-mortem examination. If our pathological examinations had revealed dosages of ketamine in excess of LD50, we would have concluded that this was a case of acute ketamine poisoning. However, toxicological examination showed much less than LD50, which leads us to conclude that this is a case of chronic poisoning using ketamine in non-lethal dosages (100 mg–300 mg per dose), administered over a period of time by which caused the observed myocardial fibrosis and hyaline degeneration of the small arteries. The large area of myocardial fibrosis resulted in heart failure and death, and some asphyxial phenomena were caused by the side effects of the last dose of ketamine. These findings are also consistent with the pathological features of chronic ketamine poisoning previously reported in animal studies by Marini et al. (4).

Finally, we conclude that the chronic ingestion of ketamine leads to myocardial fibrosis in humans and eventually causes cardiac failure. In the reported case, drug-induced cardiac damage and respiratory depression caused the victim to become inadequately oxygenated, resulting in hypoxia that led to brain death.

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