CASE REPORT

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Tissue Distribution of Ketamine in a Mixed Drug Fatality

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ABSTRACT: While reports of ketamine abuse are increasing, reports of ketamine deaths and tissue concentrations associated with fatalities are rare. We report here a case of a mixed drug fatality involving ketamine and ethanol. Ketamine analysis was carried out by gas chromatography with a nitrogen-phosphorus detector (NPD). We found the following tissue concentrations: blood 1.8 mg/L; urine 2.0 mg/L; brain 4.3 mg/kg; spleen 6.1 mg/kg; liver 4.9 mg/kg, and kidney 3.6 mg/kg. The blood ethanol concentration was 170 mg/dL. Because an empty nalbuphine ampule was found in the possession of the deceased, the blood was assayed for this opioid compound using a gas chromatography/mass spectrometry (GC/MS) method. None was detected at a limit of detection of 0.02 mg/L.

KEYWORDS: forensic science, ketamine, nalbuphine, mixed drug fatalities

Ketamine hydrochloride is marketed as an anesthetic for human and veterinary use. The only labeled uses of the veterinary product are in cats and monkeys for short-duration immobilization. While its use in human surgery has been limited by its cardiovascular-stimulating properties and high incidence of disturbing emergence reactions (1), it remains popular to include it in military field medical kits/field hospital inventories because the field medic on assignment in remote locations is often called upon to perform a variety of procedures, including veterinary procedures, for the host country population. Additionally, ketamine provides a non-controlled agent which can function as a sole anesthetic due to its unique sedative, amnestic and analgesic properties.

Chronic administration of ketamine or repeated exposure to the drug such as occurs with radiotherapy or burn patients, has led to the development of tolerance to the analgesic effects (1). Ketamine also maintains self-administration behavior similarly to central nervous system (CNS) depressant drugs (2). Therefore, the increased frequency of ketamine abuse reports are not surprising (3). Often called "K" or "Special K," ketamine produces effects similar to those produced by phencyclidine (PCP) with the visual effects of LSD.

The appearance of anecdotal accounts of ketamine abuse in teenagers' reports of "rave parties," increasing arrests for "driving under the influence" involving ketamine and burglaries of ketamine from veterinary clinics are evidence of increasing abuse and have caused the Drug Enforcement Agency (DEA) to reevaluate the non-controlled/scheduled status of the drug. Because of this increasing attention being generated by ketamine and the relative lack of toxicological case report data, we present a case of a "mixed drug" fatality involving ketamine.

Case History

A 32-year-old, active duty Army, Caucasian male, was found at 05:00 hours seated on his cot with his upper body slumped forward across his knees. A compressed 10cc syringe with a 21-gauge, $1^1/_4$-inch needle was stuck in the left antecubetal fossa. Resuscitative attempts were begun, however the subject was declared dead at 05:20 hours. A nearly empty bottle of Ketamine-HCl was found next to the body. An empty 1 mL ampule (10 mg/mL) of Nubain (nalbuphine HCl) was found in his rucksack. The decedent had been drinking with friends from 20:00 hours until 01:30 hours and was last seen alive at approximately 02:00 hours. Autopsy findings were unremarkable. Specimens were submitted for toxicological analysis.

Experimental

Materials

Ketamine hydrochloride standard was obtained from U.S.P.C., Inc. (Rockville, MD). The nalbuphine standard was obtained from Endo Laboratories, Inc. SK&F #525-A (Proadifen) was purchased from Smith, Kline and French Laboratories (Philadelphia, PA). All other reagents were J.T. Baker Reagent grade and solvents were Fisher Optima grade.

Extraction Methods

Ketamine—Samples, calibrators (0.05, 0.2, 0.5, 1.0, and 2.0 mg/L) and controls were extracted from 2 mL blood and urine or 2 g homogenized tissue. 0.1 mg/mL working standards were prepared from 1 mg/mL stock ketamine standards (in methanol). To prepare the blood control, 100 μL of a 60 mg/L methanolic working

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control were added to 2 mL of negative control blood yielding a concentration of 3.0 mg/L ketamine.

Fifty μL of 0.1 mg/mL SK&F #525-A (internal standard) were added to all tubes. Four drops of concentrated NH_4OH were added to each tube followed by 6 mL n-chlorobutane. Samples were rotated for 5 min followed by 5 min centrifugation to achieve phase separation.

The organic (top) layer was transferred to clean 16×100 tubes. Three mL 0.2N H_2SO_4 were added and the tubes were rotated for 5 min followed by 5 min centrifugation. The top layer (organic) was aspirated to waste and 4 drops concentrated KOH added to the remaining aqueous layer followed by 4 mL 1-chlorobutane. The tubes were once again rotated for 5 min followed by 5 min centrifugation. The top (organic) layer was transferred to 13 × 100 disposable glass test tubes, followed by evaporation to dryness in a 56°C water bath under a gentle stream of nitrogen. The residue was reconstituted in 50 μL of MeOH, vortexed and transferred to injection vials. Two microliters were injected for analysis.

Ethanol—0.5 mL blood or vitreous fluid and 2.5 mL working internal standard (2 mg/dL methyl-ethyl-ketone) were added to 23 mL headspace vials. Specimens were analyzed in duplicate. Specimens equilibrated for 30 min prior to chromatographic analysis.

Instrumentation

Ketamine analysis was performed using an Hewlett-Packard 5890 gas chromatograph equipped with a nitrogen-phosphorus detector (GC-NPD). The column was a J&W DB-5 5% phenyl-methyl-silicone fused capillary column (15 m × 0.25 mm ID × 0.25 μm film thickness). Helium was the carrier gas flowing at 1 mL/min. The injector temperature was 260°C with a detector temperature of 280°C. The oven temperature began at 110°C, was held for 1.0 min and increased at 20°C /min to 200°C for 1 min, then increased at 10°C/min to 290°C and held for 7 min. Splitless injection mode was used. This method was linear for ketamine from 0.05 to 2.0 mg/L. The lower limit of detection (LOD) was 0.01 mg/L and the lower limit of quantitation (LOQ) was 0.05 mg/L.

Ethanol analysis was performed on a Hewlett Packard 5890A gas chromatograph with a flame ionization detector interfaced with a Tekmar 7000 Headspace Analyzer and a 6′ × $^1/_8$″ 0.2% Carbowax 1500 on 60/80 Carbopak C column. The GC/headspace parameter settings were as follows: platen 60°C; transfer line 90°C; oven temperature 110°C, isothermal; injector temperature 125°C; detector temperature 165°C. The times were set as follows: sample equilibration, 30 min; pressurization, 0.3 min; injection, 0.3 min. The instrument was calibrated utilizing an aqueous volatile standard prepared in-house. The LOD was 1 mg/dL ethanol; our LOQ in postmortem cases is 20 mg/dL. The linearity range was 5–400 mg/dL.

Results

Postmortem cases received in the Forensic Toxicology Division at the Armed Forces Institute of Pathology routinely receive an immunoassay screen for drugs of abuse, a gas chromatography/headspace analysis for nine volatile substances and a screen for 12 classes of basic drugs. Ketamine was identified on the basic drug screen and subsequently quantitated.

Ketamine concentrations (fluids in mg/L, tissues in mg/kg) are listed in Table 1. Only blood and urine were analyzed for nalbuphine; none was detected in either specimen. Ethanol was the only volatile identified on the volatile screen. Ethanol concentrations were 170 mg/dL in the blood and 240 mg/dL in the vitreous fluid:

Discussion

Ketamine was originally investigated in the 1960's as an alternative intravenous (IV) anesthetic agent when wide spread use of phencyclidine (PCP, Sernyl) and its congener, cyclohexamine was precluded from Food and Drug Administration (FDA) clearance due to the undesirable production of long-lasting, postanesthetic psychotomimetic activity. This class of injectable anesthetics are often referred to as "dissociative" anesthetics, so-called because they induce anesthesia by disrupting the flow of information from the conscious to the unconscious parts of the brain, rather than the generalized "depression" of all brain centers typical of other anesthetics, such as inhalants.

Ketamine was found to produce adequate surgical anesthesia, a rapid recovery and less prominent emergence reactions and was approved for use in 1970. However, its clinical usefulness has since been limited because of its cardiovascular stimulating properties and high incidence of disturbing "emergence" reactions (1).

The psychic sensations reported during emergence from ketamine anesthesia have been characterized as alterations in mood state and body image, dissociative or "out-of-body" experiences, sensations of "floating," vivid dreams and illusions (4). Many users report their visit to "K-land" or the "K-hole" as actually better than the "trip" produced by PCP or LSD because it usually lasts for less than an hour. These "LSD-like" trips coupled with the fact that ketamine is currently not a controlled/scheduled substance have led to reports of increasing ketamine abuse (3). Tolerance, psychological dependence upon repeated daily exposure and a physical withdrawal syndrome have been demonstrated in animals and humans (5).

Ketamine has a profound stimulatory effect on the cardiovascular system, causing increased heart rate, cardiac output and arterial blood pressure (6). Even though ketamine increases coronary blood flow as well, it may be insufficient to meet the metabolic demands of the myocardium produced by the increase in cardiac work, thus leading to its toxic effect at high or repeated dosing (7). Additionally, ketamine causes a dose-dependent respiratory depression (6) especially in situations where it is given as a rapid, IV infusion (8). Respiration has been noted as apneustic, shallow and irregular immediately following administration in a variety of animals and humans.

The pattern of biodisposition of ketamine is analogous to some of the short-acting barbiturates (1). Initially, it is distributed to highly perfused tissues, including the brain, achieving levels which

TABLE 1—*Fluid and tissue concentrations of ketamine and ethanol (ND = Not done).*

	Analyte	
Fluid/Tissue	Ketamine (mg/L or mg/kg)	Ethanol (mg/dL)
Blood	1.8	170
Vitreous Fluid	ND	240
Urine	2.0	ND
Brain	4.3	ND
Spleen	6.1	ND
Liver	4.9	ND
Kidney	3.6	ND

are four to five times that of plasma (9). Subsequently, the drug is redistributed to less-well-perfused tissues. It is this redistribution that is primarily responsible for the termination of its hypnotic and anesthetic effects. Even though ketamine is extensively metabolized via N-demethylation in the hepatic cytochrome P-450 enzyme system, a large fraction of the ketamine administered remains in body tissues in unchanged form and may have significance with respect to a cumulative, toxic effect in chronic abusers and the potential for drug interactions (1).

Blood concentrations of ketamine sufficient to provide surgical anesthesia have been reported to range from 1.0 to 6.3 mg/L (10). In three reported fatal overdose cases (11–13), blood ketamine concentrations were 2.9, 7.0, and 27.4 mg/L, respectively. In the case presented here, while the blood ketamine concentration of 1.8 mg/L was well within the "anesthetic" range, the combination with ethanol proved fatal. Ethanol is generally recognized as a central nervous system and respiratory depressant (14), and thus may add to the respiratory depressant effect of ketamine. Additionally, acute ethanol ingestion has been demonstrated to inhibit most hepatic cytochrome P-450 systems. Other P-450 enzyme inhibitors, such as some of the benzodiazepines and secobarbital, have been shown to prolong the elimination half-life of ketamine and to delay recovery from ketamine anesthesia (15). It is reasonable to suggest that all of the above factors were contributory to the toxicity of ketamine. Therefore, the medical examiner reported the cause of death as ketamine and ethanol intoxication; the manner of death was accidental.

Acknowledgments

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