Case Report

Postmortem Blood Ketamine Distribution in Two Fatalities

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Abstract

Despite the reported increased use of ketamine as a recreational drug, relatively few fatalities attributed to ketamine poisoning have been documented. Two recent fatalities in which ketamine was detected are described and compared with cases previously reported in the scientific literature. Concentrations of ketamine were measured in the heart and femoral blood samples using gas chromatography with nitrogen phosphorus detection. Ketamine concentrations in a 26-year-old man whose death was attributed to ketamine intoxication were 6.9 and 1.8 mg/L in heart and femoral blood, respectively. In this case, the ketamine concentration detected in the heart blood is in agreement with the lowest concentration reported in the literature, in which ketamine intoxication was ruled as the cause of death and no other drugs were present. Ketamine concentrations in a 20-year-old man, whose death was attributed to asthma and ketamine was considered an incidental finding, were 1.6 and 0.6 mg/L in heart and femoral blood, respectively. Marked differences between heart and femoral blood ketamine concentrations were observed in both of the reported cases. This may be indicative of incomplete distribution prior to death and/or postmortem redistribution of ketamine.

Introduction

Ketamine is structurally and pharmacologically similar to the recreational drug phencyclidine (PCP), sharing its potent hallucinogenic and analgesic properties. Ketamine was first synthesized with the goal of creating an effective dissociative anesthetic agent devoid of PCP's characteristic disagreeable emergence effects. Emergence effects, however, have also limited the clinical usefulness of ketamine, albeit hallucinations, sensory distortions, and lively dream activity are less severe in nature than the violent and confused behavior demonstrated by individuals emerging from PCP-induced anesthesia.

In spite of its negative emergence effects, ketamine is indicated in some anesthetic and emergency procedures. Ketamine is unique among anesthetics in that it stimulates, rather than depresses, the cardiovascular system, and its respiratory depressant effects are comparatively mild. In Canada, this drug is indicated as the sole anesthetic agent in some short-duration surgical procedures, most often involving children, who seem to be less susceptible to the drug's adverse effects. Ketamine is also used for the induction of anesthesia prior to the administration of other general anesthetic agents or as a supplement to low potency anesthetics. Furthermore, ketamine possesses bronchodilator activity and has proven to be life saving in emergency room use for patients in status asthmaticus (3,4). In addition to its use with human patients, ketamine is also commonly employed as a veterinary anesthetic.

In addition to its legitimate uses, ketamine is also a drug of abuse commonly identified by street names such as Special K, Vitamin K, and K. Along with other drugs such as methylenedioxyamphetamine (MDMA; ecstasy) and gamma-hydroxybutyrate (GHB), ketamine has become increasingly popular with the promotion and growth of the rave culture (5). There has been an increase in the number of patients admitted to the emergency department experiencing adverse effects including tachycardia, palpitations, slurred speech, and depressed respiration following the recreational use of ketamine (1). It is the psychedelic effects that ketamine shares with PCP, including dream-like hallucinations, floating sensations, perceptions of creativity, and feelings of arousal and euphoria, that are perceived as desirable by the user and, as such, have led to its status as a drug of abuse. Additionally, the central nervous system depressant properties of ketamine, namely sedation, analgesia, and amnesia, are desirable for recreational users in non-rave settings and may be exploited in order to facilitate sexual assaults. As a recreational drug, the routes of administration include insufflation and intramuscular and intravenous injection. Because ketamine has a relatively short half-life and rapid clearance, abusers will administer sequential doses of the drug in order to maintain the psychotropic effects (6,7). Ketamine is difficult to synthesize, and illicit supplies are likely acquired from sources that are entitled to legitimately use the drug, such as hospitals and veterinary surgeons.

Despite the reported resurgence of ketamine abuse, limited literature is available on the ketamine concentrations in deaths...
attributed to fatal intoxication. There is evidence for the lethality of mixed-drug intoxication involving ketamine and ethanol (8) and ketamine with various rave-associated drugs (9). Two adult fatalities attributed to overdose with ketamine alone reported blood concentrations of 7 mg/L in a 31-year-old female (2) and 27 mg/L in an 18-year-old male (10). The sites from which the analyzed blood samples were drawn were not specified in either study.

Two recent fatalities in which ketamine was detected at the Centre of Forensic Sciences (Toronto, ON, Canada) are described and compared with cases previously reported in the scientific literature.

Case Histories

Case #1
A 26-year-old male employed at a local hospital as a respiratory technician was found dead at his residence in a kneeling position beside the bed. A rubber tourniquet was tied around the left arm of the deceased, a syringe with a needle was found under the body, and an additional syringe was found in the right hand of the deceased. Two 10-cc vials of Ketalar® (ketamine HCI, 50 mg/mL), one empty and the other half full, were found at the scene. External examination of the body revealed a hematoma below the tourniquet on the left arm and several needle puncture sites on the left wrist, as well as on the left and right antecubital fossae. Postmortem examination was unremarkable, except for acute congestion of the lungs. The death was concluded to be accidental, and the cause of death was ruled to be ketamine intoxication.

Case #2
A 20-year-old male with a history of asthma arrived home in the morning from what was described by a family member as an "all-night party". That evening, the male became short of breath and called for family members. The family found him wheezing and called paramedics. The emergency room staff found him in respiratory arrest and he subsequently died. There was no history of ketamine administration in the emergency room for treatment of status asthmaticus in this case, although this possibility cannot be conclusively ruled out. External examination revealed signs of treatment: intravenous normal saline line entering at the right antecubital fossa, endotracheal tube, and a thoracentesis catheter in the right upper anterior chest. Postmortem examination revealed stigmata of asthma, and the cause of death was ruled to be asthma.

Experimental

Drug screening
Ketamine and its major metabolite, norketamine, were identified by a general drug screening procedure capable of detecting numerous chemically basic drugs. This method, an adaptation of the procedure described by Koves and Wells (11), used a Hewlett Packard 5890 series II Plus gas chromatograph (GC) equipped with dual capillary columns (DB-5: 25 m x 0.32-μm i.d., 0.52-μm film thickness; DB-17: 15 m x 0.32-μm i.d., 0.25-μm film thickness) (Agilent Technologies, Palo Alto, CA), dual nitrogen-phosphorus detectors, and a 7673A autosampler. The oven temperature of the GC was set at 90°C for 2 min, then ramped at a rate of 6°C/min until reaching 290°C, and maintained at 290°C for 17 min. The identification of ketamine and norketamine was based on retention times relative to an internal standard (SKF 525A), and confirmation was by gas chromatography–mass spectrometry (GC–MS) (Hewlett Packard 5973 MSD).

Screening to determine the presence of morphine, cocaine and its metabolites, and salicylate was accomplished by radioimmunoassay using commercially available kits (Diagnostic Products Corporation, Los Angeles, CA).

Blood and urine were examined for ethanol and other volatiles using headspace gas chromatography with flame-ionization detection (GC–FID) (12).

Quantitation of ketamine
Stock solutions of ketamine were prepared in ethanol and stored at -16°C. A series of four ketamine working solutions was made by diluting the stock solution with ethanol. The extraction procedure for case samples, blood standards, and a blank was a modification of the screening method (11). Working solutions (50 μL) were measured into test tubes, and 2 mL of pre-screened blank blood (Canadian Blood Services) were added, resulting in standard concentrations of 0.25, 0.5, 1.0, and 2.0 mg/L. A blank sample consisting of 2 mL of pre-screened blood was measured into a test tube. A 2-mL aliquot of each case blood was added into separate test tubes. Toluene (7 mL) and ammonium hydroxide (100 μL) were added and each sample mixed by rotation for a 20-min period. The mixtures were centrifuged for 10 min (2800 rpm at 10°C), and the organic layer was separated for further extraction. Sulfuric acid (2N, 2 mL) was added to the organic layer, and the samples were vortex mixed for 60 s and centrifuged for 10 min (2800 rpm at 10°C). The aqueous layer was retained and the organic layer discarded. After the resultant extracts were cooled at -16°C for 10 min, they were made alkaline by drop-wise addition of 5N sodium hydroxide. Toluene (1 mL) was added to the samples, which were then vortex mixed for 60 s and centrifuged for 5 min (2800 rpm at 10°C). The organic phase was transferred to an automatic injector vial (Chromacol 1.1 autosampler microvials, VWR, Edmonton, AB, Canada) that was sealed with a Teflon-lined cap.

The samples were analyzed using a Hewlett-Packard 5890 series II GC equipped with nitrogen-phosphorus detectors and a 7673A autosampler. The columns used were a DB-1 megabore column (10 m x 0.53-mm i.d., 1.5-μm film thickness; Agilent Technologies) maintained at a temperature of 160°C and an FFAP widebore column (10 m x 0.53-μm i.d., 1.0-μm film thickness; Agilent Technologies) maintained at a temperature of 170°C.

Ketamine concentrations were measured from a calibration curve derived from the blood standards. Concentrations were determined using linear regression. The limits of detection...
and quantitation for the ketamine method were 0.06 and 0.12 mg/L, respectively. Case samples were diluted where necessary in order to bring the concentration within the limits of the standard curve.

Results

The concentrations of ketamine and other drugs determined in the two cases are listed in Table 1. Although norketamine was identified by GC–MS, it was not quantitated because of the lack of an authentic standard. The drug screening procedure used in this study was capable of identifying more than 150 drugs. With the exception of low concentrations of ethanol, no drugs other than ketamine were detected in either case sample.

Discussion

Despite reports of a recent increase in ketamine abuse, there is limited published information regarding fatal blood ketamine concentrations. Ketamine is rarely encountered in the biological samples analyzed at this laboratory, which services the province of Ontario (population: approximately 12 million people). In the year 2000, only 5 out of the 1950 GC–MS drug screening analyses performed in this laboratory detected the presence of ketamine and/or its active metabolite norketamine. The frequency of ketamine detection in the three previous years was identical. The vast majority of the cases analyzed with this laboratory's drug screening procedure were unexplained death investigations. From this we cannot determine whether or not ketamine use in the general population is widespread. However, if there is a high risk of fatality associated with ketamine use, and if ketamine use in Ontario has increased over this time period (as has been suggested for other geographical areas in North America) (1,5), one may expect that the frequency of ketamine detection in unexplained death cases would increase.

Ketamine is primarily acquired for abuse through sources such as hospitals and veterinary surgeons that have ketamine available for therapeutic use. Interviews conducted with ketamine abusers in Scotland reported that illicit ketamine was usually obtained through diversion from legitimate sources (13). The ease of acquisition and slight chance of detection through the knowledge of the short half-life of ketamine has proved to contribute to the ketamine dependence of anesthesia providers (14). There are several other reports of health care workers abusing ketamine obtained from their place of employment (6,15). The deceased referred to in case 1 of this study was employed as a respiratory technician at a local hospital. Ketamine would have been stored for use in this hospital for the treatment of status asthmaticus or for use as an anesthetic, and as such, may have been available to the deceased.

Numerous mixed-drug fatalities cite a variety of ketamine concentrations as contributing causes of death, all of which are markedly lower than the few reports of intoxication due to ketamine alone. In one death due to a ketamine and ethanol combination, the concentrations were reported as 1.8 mg/L and 170 mg/100 mL, respectively (8). In a study of several mixed-drug intoxications, in which ketamine was detected at concentrations ranging from 0.1 to 2.1 mg/L, the presence of other drugs such as opiates, MDMA, and methylenedioxymethylamphetamine (MDA) were concluded to be the major contributing factors in these fatalities (9). In this study, the cause of death in case 1 was attributed to ketamine intoxication. Ketamine, at a heart blood concentration of 6.9 mg/L, and ethanol, at a concentration of 14 mg/100 mL, were the only drugs detected in this case. These findings are in agreement with the lowest published fatal ketamine concentration reported in a death in which no other drugs were present (2). The only other published fatal monointoxication reported a much higher blood ketamine concentration of 27 mg/L (10).

Postmortem site-dependent differences in drug concentration are a common feature in forensic toxicology (16). Few studies report both heart and femoral blood concentrations of ketamine. Both of the cases described in this study, however, show marked differences between heart and femoral ketamine concentrations. The heart/femoral ratios in cases 1 and 2 were 3.8 and 2.7, respectively. In a study in which heart/peripheral concentration ratios for a number of drugs were compiled, blood ketamine ratios of 0.8 and 2.3 were reported (17). Marked differences between heart and femoral drug concentrations are traditionally attributed to a rise as the result of postmortem redistribution. This is a phenomenon that has been widely accepted and well described for a number of drugs including members of the tricyclic antidepressant and amphetamine drug classes. Alternatively, because ketamine can be administered by a variety of routes including intravenous and intramuscular injection, the difference between heart and femoral drug concentrations observed in the postmortem samples may be the result of incomplete distribution. When drug administration via injection to the upper part of the body results in a rapid death, the concentration within the heart blood may exceed that of a sample taken from peripheral regions of the body. This occurs when the drug has not had an opportunity to distribute in

| Table 1. Postmortem Ketamine Concentrations (mg/L) in Heart and Femoral Blood Samples |
|-------------------------------------|------------|--------|-------------|-----------------------------|
| Case 1 (ketamine death)            | Heart Blood | Femoral Blood | Heart/Femoral | Norketamine* | Other Drugs†           |
| 6.9 mg/L                            | 1.8 mg/L    | 3.8     | + ethanol: 14.0 mg/100 mL |
| Case 2 (asthma death)              | 1.6 mg/L    | 0.6 mg/L | 2.7          | ethanol: 13.0 mg/100 mL    |

* + denotes that norketamine was detected, and – denotes that norketamine was not detected.
† Ethanol was measured in femoral blood.
the blood throughout the body. Given the paucity of literature regarding postmortem ketamine distribution and because the history indicates that the deceased in case 1 was found with a tourniquet still on his arm and his death appears to have been rapid, the mechanism responsible for the observed site-dependent ketamine differences cannot be conclusively determined.

The ketamine concentrations reported in this study illustrate the importance of considering both heart and peripheral blood samples in the investigation of some fatalities. Cases involving a potentially fatal concentration of a drug that is thought to be susceptible to postmortem redistribution and cases in which there is evidence of a rapid death and incomplete distribution is thought to be a possibility that should be considered for alternate site examination. The circumstances surrounding case 1, in addition to the heart blood ketamine concentration, are indicative of a death due to ketamine intoxication. However, the femoral blood concentration in this case is much lower than concentrations found in published reports of fatalities attributed to intoxication with ketamine alone, and consideration of this femoral blood result in isolation may have led to the interpretation that ketamine was present at a sub-fatal concentration.

Given the present state of the scientific literature, the heart blood ketamine concentration in this case provides greater interpretative value than the femoral blood ketamine concentration. In cases in which heart/peripheral differences are indeed due to postmortem redistribution, the heart blood concentration would be artificially elevated and the peripheral blood concentration would, in theory, provide greater interpretative value. However, this interpretative approach would only be prudent providing there were adequate reports of potentially fatal femoral blood ketamine concentrations in the literature. Earlier reports of ketamine fatalities do not mention the site from which the analyzed blood was drawn. In these reports, it is likely that heart blood was analyzed, as this was (and in many laboratories still is) the common practice. If this is the case, there are inherent difficulties in using these reported concentrations to interpret detected peripheral blood concentrations. To our knowledge, this is the first published report of a peripheral blood ketamine concentration in a death attributed solely to ketamine intoxication. Additional reports, documenting peripheral and heart blood concentrations of ketamine, are needed in order to establish a guideline for potentially fatal peripheral drug concentrations.

Furthermore, given a history of rapid death following intravenous ketamine injection, in which incomplete distribution may be a possibility, the heart blood concentration would provide a better indication of the amount of drug being delivered to the brain and the cardiac tissue. Because ketamine’s toxicities include depression of the respiratory center of the brain and cardiac toxicity (18), the heart blood concentration would better reflect the extent of drug action at these sites than a peripheral blood concentration.

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**References**