CASE REPORT

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A Fatal Ketamine Poisoning

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ABSTRACT: An unusual case of death by ketamine overdose is reported. The drug's administration was a homicide for homosexual ends. Authors discuss a rapid and effective solid-phase extraction procedure using Bond-Elute* C18 for Ketamine and Nor-Ketamine detection in biological fluids and tissues with a 75% recovery. The drug analysis was carried out by the means of gas-chromatography (GLC) and gas-chromatography/mass spectrometry (GC-MS). The yield of the procedure for Ketamine was: blood 27.4 μg/mL; urine 8.51 μg/mL; bile 15.2 μg/mL; brain 3.24 μg/mL; liver 6.6 μg/mL; kidney 3.38 μg/mL. Nor-Ketamine was detected in all samples, but not quantified.

KEYWORDS: toxicology, poisoning, anesthetic, ketamine

Ketamine, (+− (2,2 chlorophenyl) 2-methylaminocyclohexanone), Ketalar ®, is used as a general anesthetic during surgery. It induces sedation, immobility, amnesia and deep analgesia, often called "disassociated anesthesia" because of the sensation of detachment from the surroundings perceived by the patient [*1*].

Case History

The decedent was an 18 year old white male, weighing 75 kg. He was found half-laying on the driver's seat of a locked car, parked in a remote mountainous and uninhabited area. According to liver temperature and witnesses, death occurred 12 to 16 hours before the discovery of the body. Three fresh needle marks were found on the inferior/external quadrant of the left buttock. Vials labelled Ketalar® were found on the crime scene. The total administered dose was estimated to be the equivalent of 1 g.

The postmortem examination excluded traumatic noxae and/or spontaneous pathologies as the primary cause of death. Death was attributed to massive pulmonary edema.

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The authors regret that certain details of the case history may seem imprecise or incomplete, this is due to limitations imposed by the authorities who are conducting an ongoing investigation of this case.

Toxicological Analysis

Materials

Bond-Elute® C18 bonded silica sorbent cartridges for solid phase extraction (SPE) of biological samples were supplied by Varian, Milano, Italy; all analytical grade reagents were supplied by Carlo Erba, Milano, Italy. Ketamine standard was supplied by Parke Davis Corp., Milano, Italy.

Extraction Methods

Two methods for SPE were adopted: one based on the direct extraction approach at room temperature, the other on hot acid treatment of the sample before SPE extraction. The latter was to avoid co-extraction of endogenous interfering compounds. The tests performed before such extraction included verification of the stability of ketamine to hot acid treatment; the SPE method yield when blank fluids, as well as tissue homogenates were used in the presence of standard ketamine; liquid/liquid extraction were run in parallel as quantity checks of the stated methods [*2,3*]: Bond-elut C18 6 mL cartridge: condition with 3 mL of methanol and 3 mL of water.

Preparation of the Sample—

A) blood (2 mL), urine (3 mL): add 5 mL of phosphate buffer (pH 8,5)

B) blood (2 mL), urine (3 mL), tissues (5 gr): add 1 mL conc.HCl, then 2 mL sat. ammonium sulfate and 5 mL water. Heat for 1 h at 100°C, then filter; alkalinize to pH 8.5 with NaOH.

The samples were drawn through the cartridges under 5 mm Hg of negative pressure.

Rinse of Cartridges—

3 mL of distilled water.

Final elution— chloroform/isopropanol (3:1) + 1% of NH_3.

The eluent was evaporated under nitrogen flow and reconstituted in methanol.

Instrumentation

Gas chromatography— a C.Erba 4200 gas chromatograph equipped with a Supelco SPB 35 wide bore coloumn (30 m, 0.75 mm ID, 1,0 μm film thickness), operating in the programmed range of 150°–280°C (3 min initial isotherm, 3°C/min rise, 10 min final isotherm). The flow rate of carrier (Helium) was 1 mL/min.

Gas chromatography mass spectrometry assay— Varian gas chromatograph and a SSQ 710 Finnigan mass spectrometer equipped with a J & W Scientific DB-5-MS capillary coloumn (30 m, 0.25 mm ID, 1.0 μm film thickness), operating at the previous mentioned conditions. A full mass spectrum scan of 45 to 650 m/z was employed for identification purposes (Fig. 1).

Results

The good fit of the resulting curves and the high yield of the Ketamine (about 75%) from blank postmortem blood, provided verification of the accuracy of the SPE methods. Eluates obtained by method b were cleaner for tissue samples.

Quantitative evaluation was performed with an internal standard (lignocaine). The method's accuracy for blood was about 50 ng/mL. The SPE (Fig. 2) and liquid/liquid extraction systems were adopted with the purpose of establishing a mutual check and to achieve

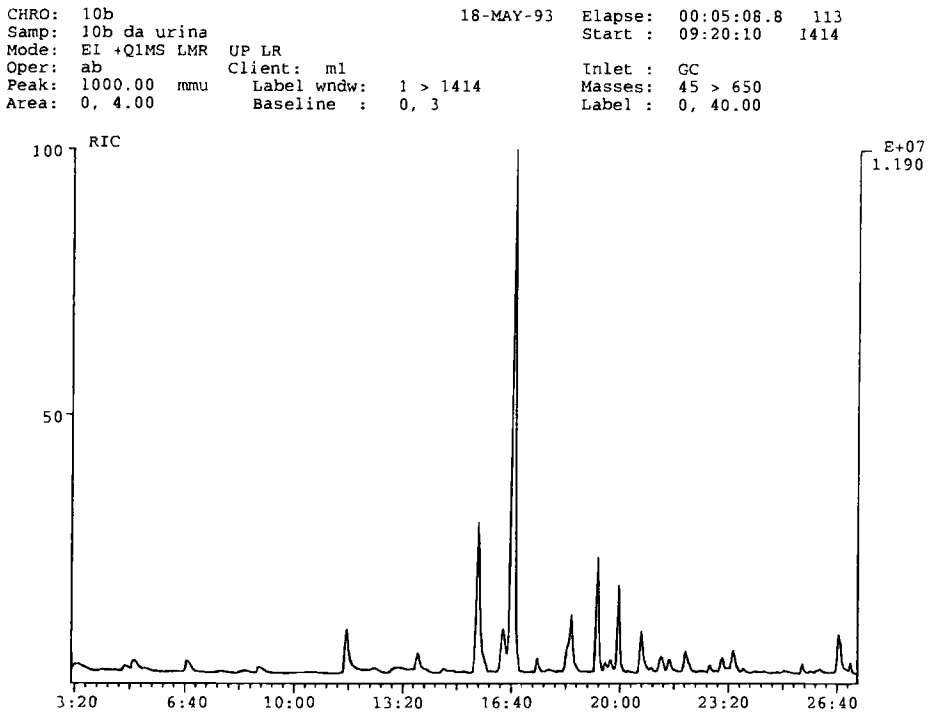

FIG. 1—*Total ion chromatogram of a urine extract.*

greater complementarity between the two methods, especially concerning qualitative measurements of metabolites, the extraction efficacy and their stability during the operations. The liquid-liquid extraction (which reveals the major number of co-extracted compunds) was used with the intent to exclude eventual losses of Ketamine methabolites during the SPE procedure. Nor-Ketamine was the only methabolite to be detected and extracted with both methods.

Analysis for determination of the norketamine metabolite with GC-MS was carried out with and without derivatization according to the methods of Centini et al. [*3*].

Of note, the GC-MS analysis of the non-derivatized specimens revealed significant ketamine ions at m/z 237(Im), 209(-CO), 180(-C2H4), and 152(-NHCL), as well as at m/z 223, 195, 166, 150, for the corresponding norketamine mass spectra (Fig. 3–4).

Discussion

During the study of this case certain new elements emerging from the recent international literature were considered, such as the theories of Geisslinger and Peyton [*4,5*]. The former contends that the dehydronorketamine metabolite is a gas-chromatographic artifact and that the "emergency reactions" (cardio-vascular stimulation, hallucinations) of the drug are due to the R enantiomeric form. Peyton [*5*], treating a case of acute ketamine intoxication, compared it to a case of therapeutic treatment with the same drug and thus arrived at three observations of particular interest:

1) that the hematic concentration in cases of overdose are not significantly different from control cases (deceased for other reasons);

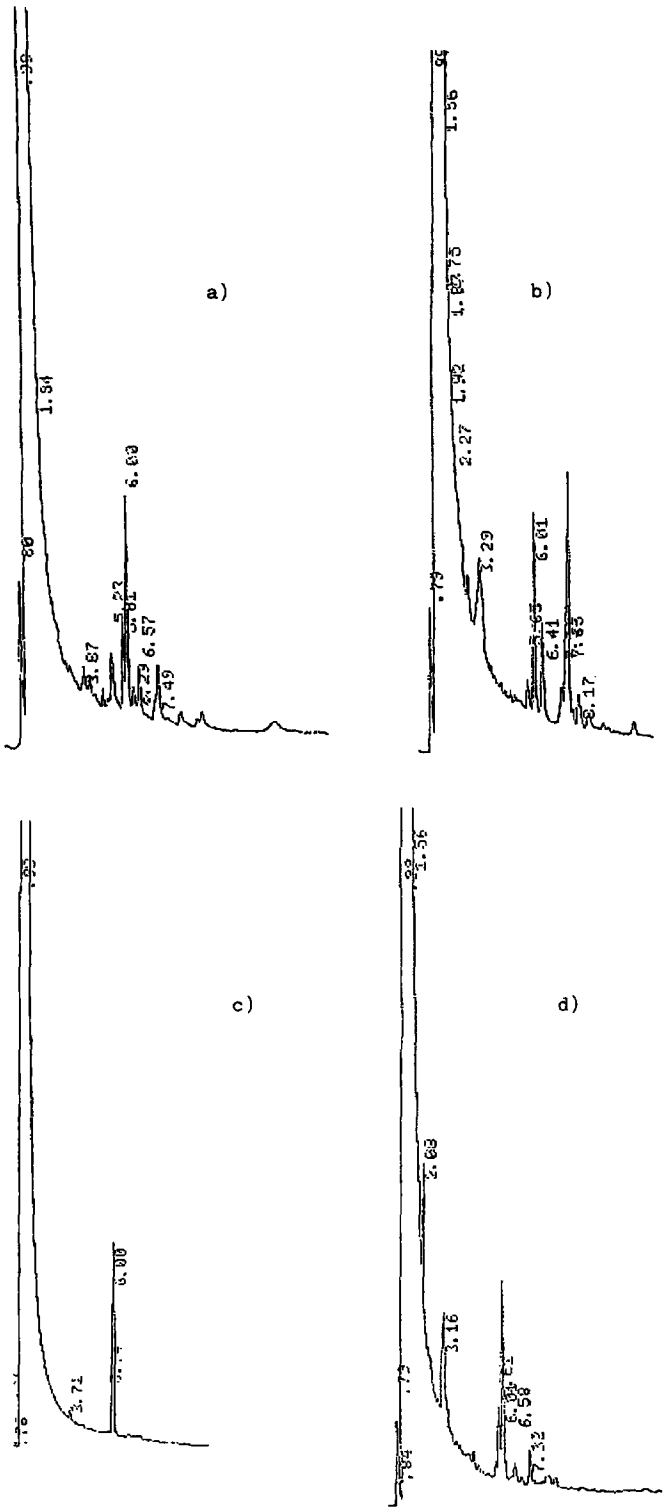

FIG. 2—*Gas-chromatogram of victim's brain tissue [a], urine [b], and blood [d], and of standard Ketamine [c].*

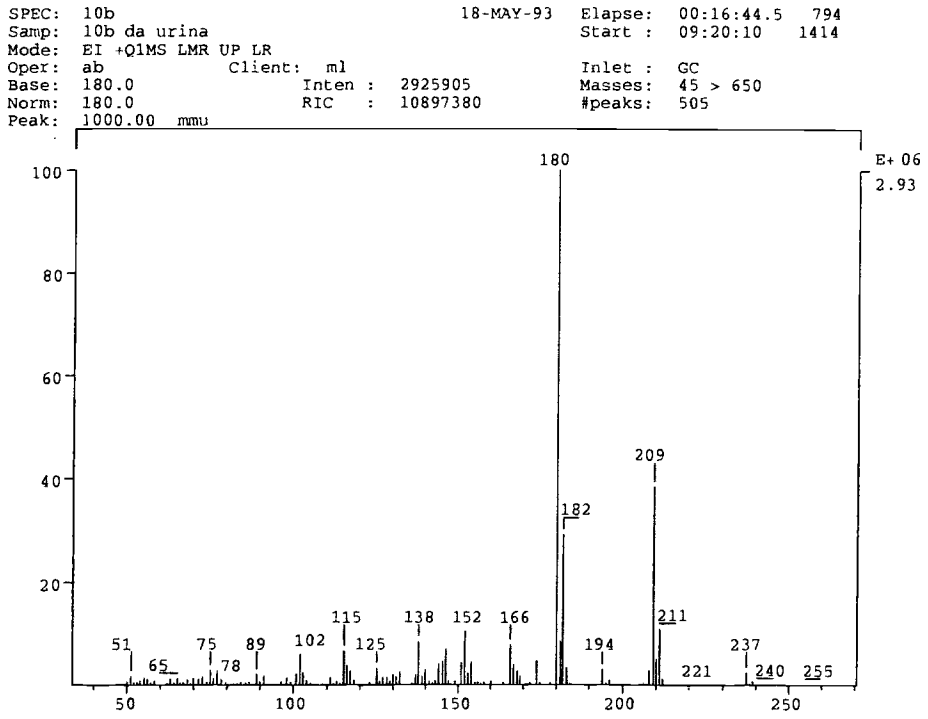

FIG. 3—*Mass spectrum of Ketamine.*

2) that the presence of norketamine implies an interval of time between administration and death; and

3) that the high kidney and liver concentrations are consistent with administration of a lethal dose followed by a period of survival permitting the establishment of equilibrium distribution of the drug throughout the body.

The measured tissue and fluid concentrations (Table 1) are similar to those reported by Peyton [*5*] and slightly less than those reported by Centini except for the brain [*3*]. The similarities with Peyton's [*5*] observations are significant, that is, the presence of a considerable quantity of the drug in the tissues (the same range as the values reported by Peyton [*5*]. Nevertheless, the high blood concentration is strikingly different from that reported by Peyton. It is important to note that norketamine was detected in all fluids and tissues examined, but not quantified.

TABLE 1—*Drug recovery from body fluids and tissues.*

Specimen	Quantity of ketamine (μg/mL (g))
Blood	27.40
Urine	8.51
Bile	15.20
Brain	3.24
Liver	6.60
Kidney	3.38

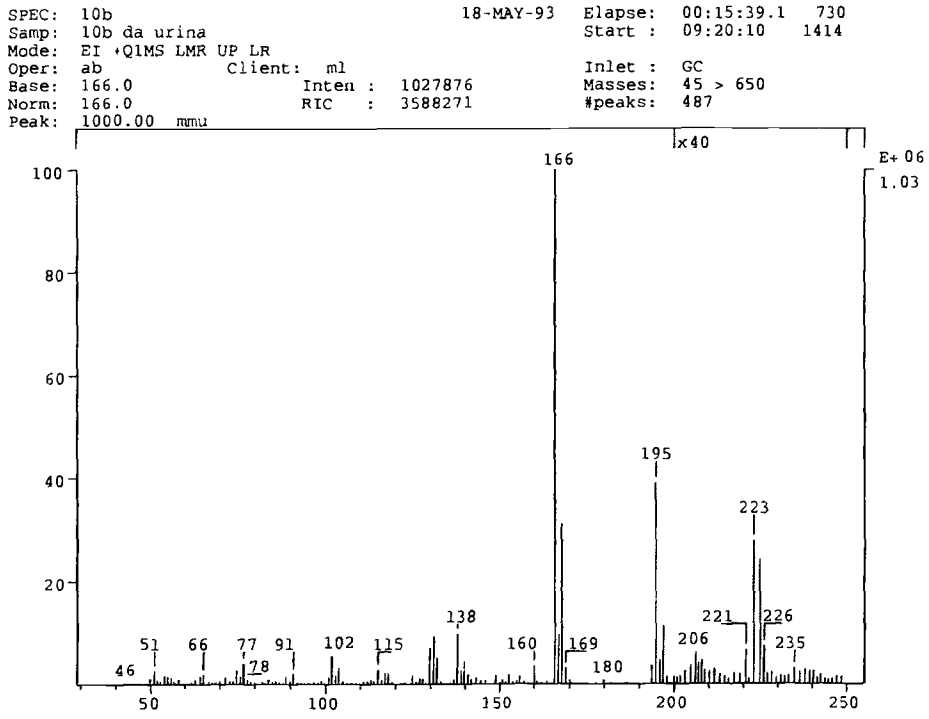

FIG. 4—*Mass spectrum of underivatized norketamine.*

The cause of death was determined to be due to Ketamine overdose based on pathology and toxicology findings.

Considering the high blood level of the drug, the number of needle marks and the suspect's incomplete personal account of the episode, it is likely that two or more doses of the drug were administered, the last shortly before death. In addition, according to Peyton [5], as reported, the finding of norketamine in fluids and tissues and the high levels of ketamine in the liver and kidneys lead to the conclusion that a long period of time elapsed between the first administration and the victim's death.

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References

[1] Goodman Gilman, A., Rall, A. T., Nies, A. S., and Taylor, P., *Le Basi Farmacologiche Della Terapia.* VIII Ed., Zanichelli, Bologna, 1992.

[2] Kintz, P., Mangin, P., Lugnier, A. A., and Chaumont, A. J., "Dosage de la Ketamine dans les Liquides Biologiques," *Cahiers d'Anesthésie.*, Vol. 38, No. 3, 1990, pp. 173–174.

[3] Centini, F., Gabbrielli, M., Fineschi, V., and Comparini Barni, I., "Fatal Ketamine Abuse: Report of a Case and Analytical Determination by Gas Liquid Chromatography, Mass Spectrometry," *Developments in Analytical Methods in Pharmaceutical, Biomedical and Forensic Sciences,* Plenum Publishing Corporation, 1987, pp. 147–153.

[4] Loscher, W., Ganter, M., and Fassbender, C. P., "Correlation Between Drug and Metabolite Concentrations in Plasma and Anesthetic Action of Ketamine in Swine," *American Journal of Veterinary Research,* Vol. 51, No. 3, 1990, pp. 391–398.

[5] Peyton, S. H., Couch, A. T., and Bost, R. O., "Tissue Distribution of Ketamine: Two Case Reports," *Journal of Analytical Toxicology,* Vol. 12, 1988, pp. 268–269.

[6] Ashleigh, E. A., Peskind, E. R., Veith, R. C., and Dorsa, D. M., "Desimipramine Potentiates Anesthetic and Lethal Effects of Ketamine," *Anaesthesia and Analgesia,* Vol. 70, 1990, pp. 571–572.

[7] Baselt, R. C., *Disposition of Toxic Drugs and Chemicals in Man,* Biomedical Publications, Davis, Cal., 3rd Ed., 1989.

[8] *Clarke's Isolation and Identification of Drugs,* The Pharmaceutical Press, London, 2nd Ed., 1986, p. 694.

[9] Dill, W. A., Chucot, L., Chang, T., and Glazko, A. J., "Determination of Ketamine in Blood Plasma," *Laboratory Methods,* Vol. 34, No. 1, pp. 74–76.

[10] Geisslinger, G. and Menzel-Soglowek, S., "Stereoselective High-Performance Liquid Chromatographic Determination of Enantiomers of Ketamine and Norketamine in Plasma," *Journal of Chromatography,* Vol. 568, 1991, pp. 165–176.

[11] Ghoneim, M. M. and Korttila, K., "Pharmacokinetics of Intravenous Anaesthetics: Implication for Clinical Use," *Clinical Pharmacokinetics,* Vol. 2, 1977, pp. 344–372.

[12] Goldenthal, E. J., "A Compilation of LD_{50} Values in Newborn and Adult Animals," *Toxicology and Applied Pharmacology,* Vol. 18, 1971, pp. 185–207.

[13] Greene, C. A., Gillette, P. C., and Fyfe, D. A., "Frequency of Respiratory Compromise After Ketamine Sedation for Cardiac Catheterization in Patients < 21 years of Age," *The American Journal of Cardiology,* Vol. 68, No. 15, pp. 1116–1117.

[14] Hannalata, R. S. and Patel, R. I., "Low Dose Intramuscular Ketamine for Anesthesia Pre-Induction in Young Children Undergoing Brief Outpatient Procedures," *Anesthesiology,* Vol. 70, 1989, pp. 598–600.

[15] Haskins, S. C. and Klide, A. M., "Precaution When Using Ketamine for Induction of Anesthesia," *Injectable Anesthetics,* pp. 268–269.

[16] Karajan, J., Lacoste, L., and Breuil, K., "Allergie a la Ketamine," *Annales Françaises d'Anesthésie et de Réanimation,* Vol. 9, 1990, pp. 396–397.

[17] Koppel, C., Asndt, J., and Ibe, K., "Effects of Enzyme Induction, Renal and Cardiac Function on Ketamine Plasma Kinetics in Patients with Ketamine Long-Term Analgosedation," *European Journal of Drug Metabolism and Pharmacology,* Vol 15, No. 3, 1990, pp. 259–263.

[18] Mereto, G. C., Quarati, A., and Baldini, C., "Osservazioni sulla Tossicità Acuta dei Farmaci Anestetici: Valutazione e Sintesi delle Nostre Ricerche," *Minerva Anestesiologica,* Vol. 45, 1979, pp. 97–101.

[19] Rioux, J., "La Ketamine (Ketalar®) Etude Pharmacologique et Clinique," *Annales de Anesthesie Françaises,* Vol. 16, No. 2, 1975.

[20] Stowe, D. F., Bosniak, Z. J., and Kampine, J. P., "Comparison of Etomidate, Ketamine, Midazolam, Propofol and Thiopental on Function and Metabolism of Isolated Hearts," *Anesthesia and Analgesia,* Vol. 74, 1992, pp. 547–558.

[21] Wright, M., "Pharmacological Effects of Ketamine and Its Use," *Journal of the American Veterinary Medical Association,* Vol. 180, No. 12, 1982, pp. 1462–1471.

[22] Write, P. F., Way, W. L., and Trevor, A. J., "Ketamine. Its Pharmacology and Therapeutic Uses," *Anesthesiology,* Vol. 56, 1982, pp. 119–136.

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