

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; alkalize 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 NH₃.

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 column (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 column (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

CHRO: 10b	18-MAY-93	Elapse: 00:05:08.8	113
Samp: 10b da urina		Start : 09:20:10	1414
Mode: EI +QIMS LMR	UP LR		
Oper: ab	Client: ml	Inlet : GC	
Peak: 1000.00 mmu	Label wndw: 1 > 1414	Masses: 45 > 650	
Area: 0, 4.00	Baseline : 0, 3	Label : 0, 40.00	

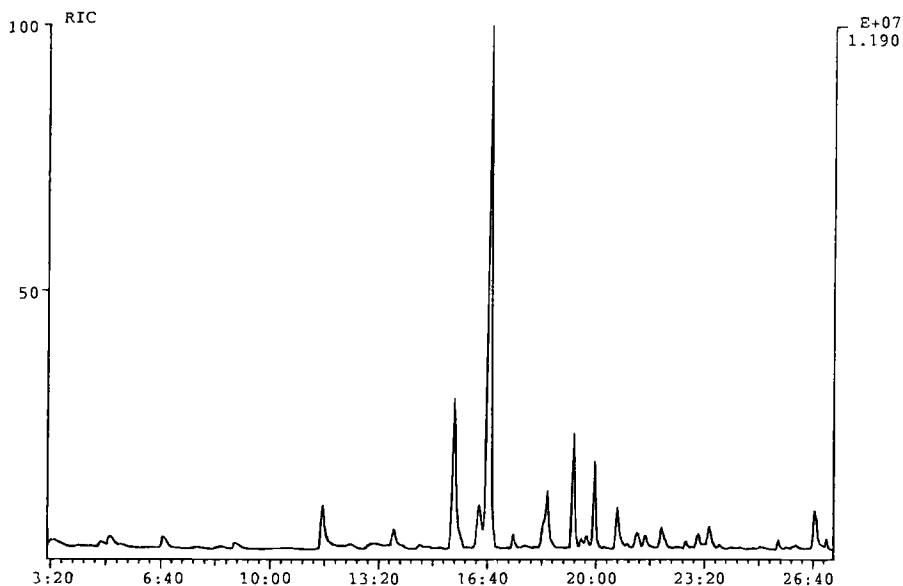


FIG. 1—Total ion chromatogram of a urine extract.

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 compounds) was used with the intent to exclude eventual losses of Ketamine metabolites during the SPE procedure. Nor-Ketamine was the only metabolite 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);

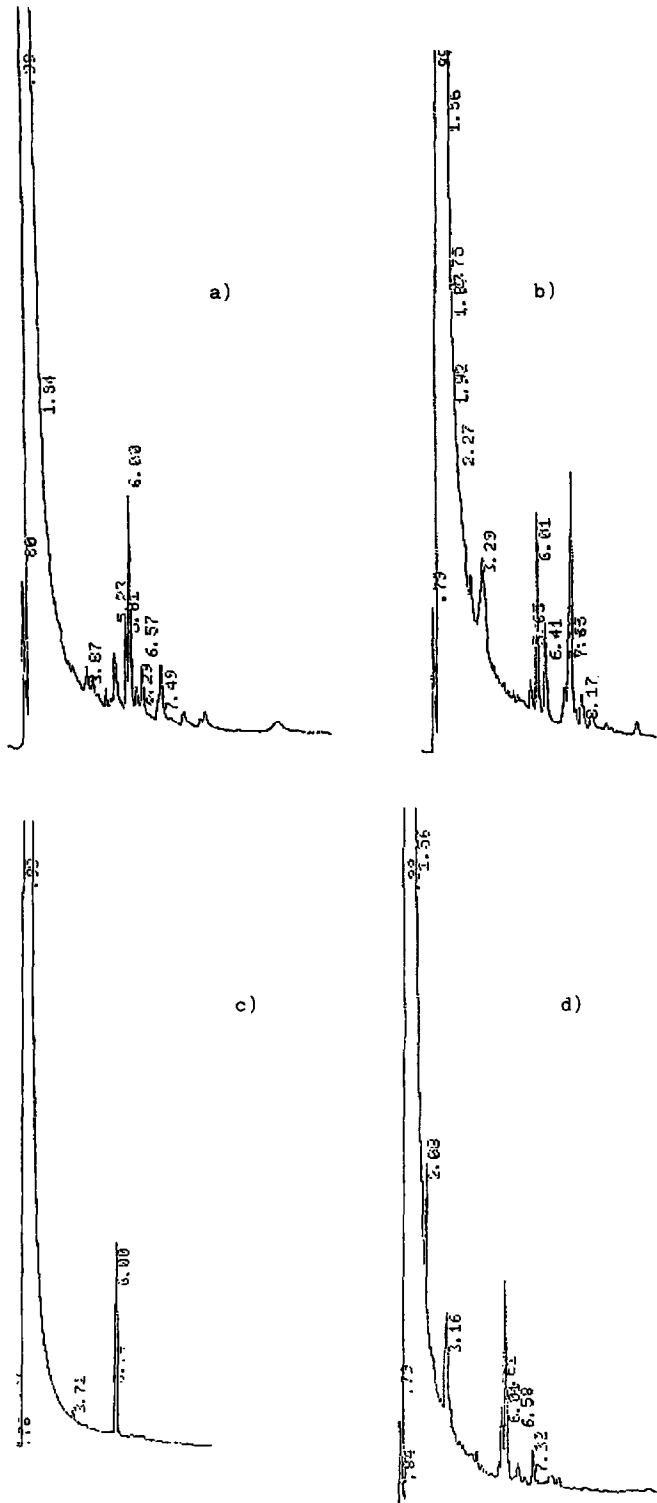


FIG. 2—Gas-chromatogram of victim's brain tissue [a], urine [b], and blood [d], and of standard Ketamine [c].

SPEC: 10b 18-MAY-93 Elapse: 00:16:44.5 794
 Samp: 10b da urina Start : 09:20:10 1414
 Mode: EI +Q1MS LMR UP LR
 Oper: ab Client: ml Inlet : GC
 Base: 180.0 Inten : 2925905 Masses: 45 > 650
 Norm: 180.0 RIC : 10897380 #peaks: 505
 Peak: 1000.00 mmu

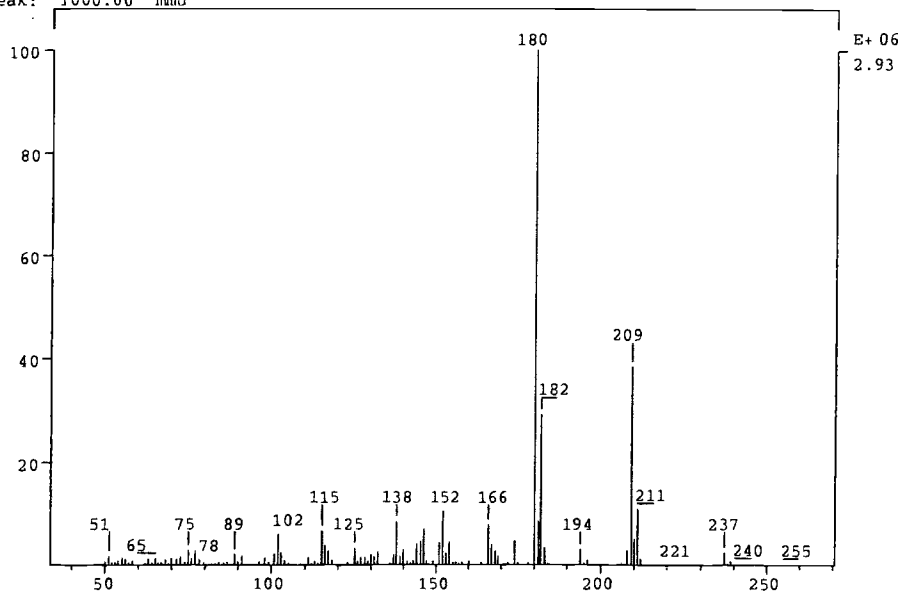


FIG. 3—Mass spectrum of Ketamine.

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 ($\mu\text{g/mL}$ (g))
Blood	27.40
Urine	8.51
Bile	15.20
Brain	3.24
Liver	6.60
Kidney	3.38

SPEC: 10b 18-MAY-93 Elapse: 00:15:39.1 730
 Samp: 10b da urina Start : 09:20:10 1414
 Mode: EI +Q1MS LMR UP LR
 Oper: ab Client: ml Inlet : GC
 Base: 166.0 Inten : 1027876 Masses: 45 > 650
 Norm: 166.0 RIC : 3588271 #peaks: 487
 Peak: 1000.00 mmu

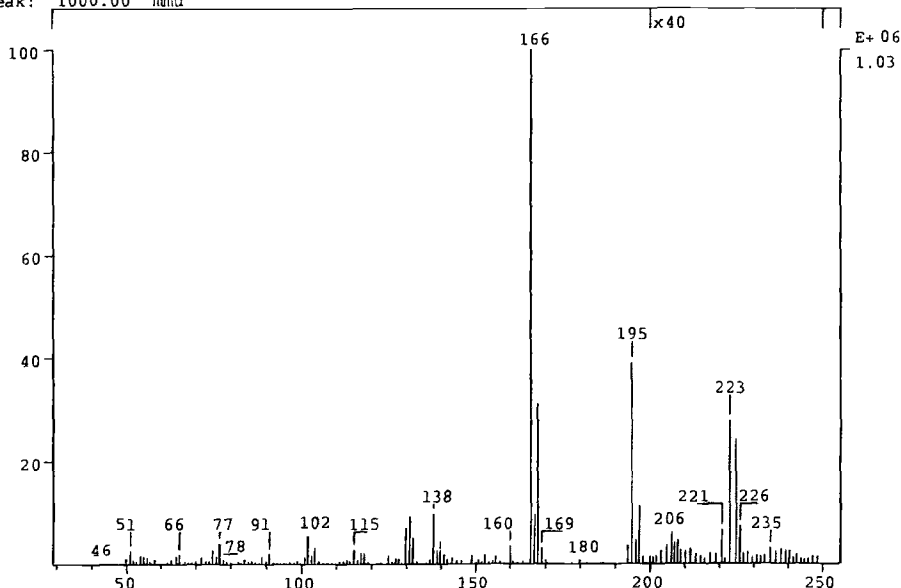


FIG. 4—Mass spectrum of underivatized norketamine.

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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