CASE REPORT

Olaf H. Drummer, Ph.D.(Melb).[1]

A Fatality Due to Propofol Poisoning

REFERENCE: Drummer, O. H., **"A Fatality Due to Propofol Poisoning,"** *Journal of Forensic Sciences*, JFSCA, Vol. 37, No. 4, July 1992, pp. 1186–1189.

ABSTRACT: This report describes a suicide by self-administration of propofol in a 29-year-old female radiographer. This is the first published report of death by overdosage with propofol. Propofol was detected in tissues using high performance liquid chromatography. Post mortem femoral blood and liver concentrations of propofol were 0.22 mg/L and 1.4 mg/kg, respectively. The scene suggested that a dose of 400 mg was used.

KEYWORDS: toxicology, propofol, blood, tissues, HPLC

Propofol (Diprivan^{R}) is a recently marketed intravenous induction agent for anesthesia [*1*]. Chemically, propofol is 2,6-di-isopropylphenol, which is quite different from other short-acting anesthetics structurally. Propofol is a highly lipophilic agent with a fast onset and long duration of action [*1*]. Death associated with a fatal overadministration of propofol has not been reported before in the literature. A death associated with self-administration of propofol by a female hospital radiographer is described.

Case Note

The deceased was found slumped over a bed in the main bedroom of her home. A hypodermic needle attached to a length of surgical tubing (catheter) was found inserted in the dorsum of the right foot. Two empty 20 mL ampoules of Diprivan, a number of new and used syringes, and two used ampoules of sodium chloride solution were found next to the body. The deceased was a 29 year old female of slim build weighing 57 kg who was employed as a radiographer at a major public hospital and had access to this drug. She had previously been known to use the drug intravenously at home and according to a friend had called it "the milk of human kindness."

Internal macroscopic examination showed no pathological abnormality in the cardiovascular system, gastrointestinal tract, endocrine, or haemopoietic systems. The lungs were moderately congested with occasional petechial hemorrhages on the pleural surface. The brain showed diffuse post mortem softening but no focal lesions were identified.

Material and Methods

Sample Preparation

Liver (10 g) was finely diced and homogenized for 15 min in 10 mL of distilled water using a Stomacher Lab-Blender 80 (Seward Medical VAC). The pH was adjusted to 10

Received for publication 6 Sept. 1991; revised manuscript received 23 Oct. 1991; accepted for publication 18 Nov. 1991.

[1]Assistant Director (Scientific Services), Victorian Institute of Forensic Pathology, South Melbourne, Victoria, Australia and honorary senior lecturer in Forensic Medicine, Monash University.

with sodium hydroxide solution and digested for 2 h at 55°C with 10 mg subtilisin (Sigma). Following digestion, the pH of the liver homogenate was adjusted back to 7. Muscle tissue (1.5 g) taken from the injection site was finely diced and homogenized for 2 h in 15 mL of distilled water using the Lab-Blender.

Urine (0.25 mL) was added to 250 μL of 1.1 M sodium acetate buffer, pH 5.1 and hydrolysed with 5000 units of B-glucuronidase (Patella Vulgata, Sigma) by incubating at 37°C for 2 h.

The needle and cannula, which were still present in the injection site, were also submitted for analysis. Methanol was slowly flushed through the needle and cannula. An aliquot of the methanol wash, after centrifugation, was injected into the HPLC.

Propofol was extracted from post mortem blood, liver homogenate, muscle homogenate, and from both unhydrolyzed and glucuronidase-hydrolyzed urine essentially as that described previously [*2*]. Standards containing known amounts of propofol (0, 2, 4, and 8 mg/L) were prepared in drug-free blood, liver homogenate, and urine. Blank samples of all these tissues were included in the run. Both blank samples and standards were extracted at the same time and treated in the same way as the unknown tissues.

Chromatography

Chromatography was performed isocratically using a LC-6AD pump and variable wavelength UV detector (Shimadzu Instruments) set at 270 nm. A rheodyne loop injector was used for sample injection. Integration and plotting was performed on a CR6A integrator (Shimadzu). The mobile phase consisted of acetonitrile, methanol, water (50:10:40) pumped at 2 mL/min through a 10 cm by 0.38 mm I.D. 5S-ODS2 stainless steel column (Phase Separations). The retention time of propofol was 5 min.

Toxicology

In addition to the measurement of propofol, a full toxicological screen was also conducted. This included an immunoassay screen in urine for the drugs-of-abuse, amphetamines, cocaine, opiates, methadone, and cannabinoids. Blood was also subjected to screening for alcohol, trichloroethanol (chloral hydrate metabolite), nitrogenous bases on a BP-5 capillary column in a gas chromatograph with nitrogen phosphorous detection [*3*] and screening for acid-neutral drugs on a photodiode array gradient-elution HPLC technique [*4*].

Benzodiazepines that were detected in urine following enzyme-multiplied immunoassay (EMIT) were identified and quantified in blood using HPLC [*5*].

Results and Discussion

Propofol was detected in viscera using HPLC. Propofol gave a sharp peak eluting at 5 min resolved from other components in the chromatogram. The recovery of propofol from blood and liver homogenate was 52 and 50% at 8 mg/L (n = 3) respectively. This was assessed by comparing the peak area obtained of an unextracted standard to extracted standards prepared by adding known amounts of propofol to drug-free tissues prior to extraction. The detection limit of propofol in these tissues was 0.1 mg/L.

Propofol was detected in large amounts in the muscle tissue around the needle taken from the right dorsum (Table 1). Propofol was also detected in the needle and surgical tubing. An aliquot of the methanol extract from the surgical tubing was subjected to gas chromatography-mass spectrometry. Mass spectral analysis (electron impact) confirmed the presence of propofol. The major ions detected were m/z 163 (100%), 178 (80%), 117 (43%), and 91 (32%). Propofol was also detected in liver and relatively large amounts

TABLE—*Summary of toxicological findings.*

Propofol	
Femoral blood	0.22 mg/L
urine (unhydrolyzed)	5.4 mg/L
urine (hydrolyzed)	94 mg/L
liver	1.4 mg/kg
muscle	222 mg/kg
needle and cannula	1.3 mg
Oxazepam	
blood	0.03 mg/L
Benzodiazepines	
urine	Detected

of glucuronide conjugates of propofol were found in urine (Table 1). Formation of glucuronides are consistent with the known metabolism of propofol, [*1*,*2*]. A small amount of the benzodiazepine oxazepam was also detected. It is unlikely that this amount, which represents only a fraction of a usual therapeutic concentration, would have contributed to the death.

Recommended doses of propofol in un-premedicated patients are 2 to 2.5 mg/kg given as a titration infusion over approximately 30 min until anesthesia occurs [*1*,*6*]. In a person of weight 57 kg a dose of approximately 110 to 140 mg may be required for induction. At the scene of death, two empty vials of Diprivan were found. This would translate to a maximum dose of 400 mg (200 mg per vial), approximately three times the recommended dose for induction of anesthesia.

Blood concentrations of propofol following a single bolus induction dose are generally less than 1 mg/L and at 100 min post dose concentrations are approximately 0.2 mg/L. However blood concentrations of propofol following multiple bolus dose or continuous intravenous infusions may reach values higher than 5 mg/L [*1*].

Assuming a large intravenous bolus dose, the blood concentrations would have most probably been in excess of that required for onset of unconsciousness [*6*]. The onset of unconsciousness and CNS depression are also known to be related to the speed of injection. Accidental overdosage is reported in the prescribing literature to cause respiratory depression. Other adverse reactions to propofol include hypotension and convulsions. It is likely therefore that unconsciousness occurred fairly quickly in the deceased after injection. The relatively high amounts of glucuronide conjugates of propofol suggest either that death was not instantaneous or that the deceased had previously used propofol. There is good evidence to suggest she had been using this drug regularly since her friend had seen her unconscious on two previous occasions following intravenous use of Diprivan and she had mentioned Diprivan to her boyfriend many months before her death.

The coroner returned the finding that the deceased died from an overdose of propofol and that there was no indication that she intended to take her own life or that any second party was involved.

Acknowledgment

I thank the State Coroner of Victoria for making his files available.

References

[1] Cockshott, I. D., "Propofol ('Diprivan') Pharmacokinetics and Metabolism—an Overview," *Postgraduate Medical Journal*, Vol. 61, (Suppl. 3), 1985, pp. 45–50.
[2] Vree, T. B., Baars, A. M., and De Grood, P. M. R. M., "High-Performance Liquid Chromatographic Determination and Preliminary Pharmacokinetics of Propofol and its Metabolites in Human Plasma and Urine," *Journal of Chromatography*, Vol. 417, 1987, pp. 458–464.
[3] Eklung, A., Jonsson, J., and Schuberth, J., "A Procedure for Simultaneous Screening and Quantification of Basic Drugs in Liver, Utilizing Capillary Gas Chromatography and Nitrogen Sensitive Detection," *Journal of Analytical Toxicology*, Vol. 7, 1983, pp. 24–28.
[4] Drummer, O. H. and Kotsos, A., "A Class-Independent Drug Screen in Forensic Toxicology Using a Photodiode Array Detector," Proceedings of the International Association of Forensic Toxicologists, Oct. 1990.
[5] Dusci, L. J. and Hackett, L. P., "Simultaneous Estimation of Clobazam, N-Desmethyl Clobazam and Clonazepam in Plasma by High Performance Liquid Chromatography," *Therapeutic Drug Monitoring*, Vol. 9, 1987, pp. 113–116.
[6] Kanto, J. and Gepts, E., "Pharmacokinetic Implications for the Clinical Use of Propofol," *Clinical Pharmacokinetics*, Vol. 17, 1989, pp. 308–326.

Address requests for reprints or additional information to
Olaf H. Drummer, Ph.D., (Melb.).
Victorian Institute of Forensic Pathology
57-83 Kavanagh Street
South Melbourne, Victoria 3205 Australia