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CASE REPORT

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Death after excessive propofol abuse

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Abstract Abuse of the anaesthetic agent propofol (2,6-diisopropylphenol) is rare, but we report a case of a 26-year-old male nurse in which the autopsy showed unspecific signs of intoxication and criminological evidence pointed towards propofol abuse and/or overdose. Intravenously administered propofol is a fast and short-acting narcotic agent, therefore it seemed questionable whether the deceased would have been able to self-administer a lethal overdose before losing consciousness. The blood and brain concentrations corresponded to those found 1–2 min after bolus administration of a narcotic standard dose of 2.5 mg propofol/kg body weight. Extremely high propofol concentrations were found in the urine indicating excessive abuse before death. However, due to the short half-life of propofol, the cumulative effects of repeated injections should not be relevant for toxicity, since this would result in a blood level increase of only 1–2 μg/ml. Furthermore, the detection and quantitation of propofol in three different hair segments indicated chronic propofol abuse by the deceased. The results of the investigation suggest that death was not caused by a propofol overdose but by respiratory depression resulting from overly rapid injection.

Keywords Propofol abuse · Fatality · Propofol overdose · Hair analysis · Brain concentration

Introduction

Propofol is a new short-acting anaesthetic used for inducing and maintaining general anaesthesia. It has no affinity to opiate, benzodiazepin, or NDMA receptors and thus should not have the potential for abuse or addiction that is always associated with the risk of overdose, as in the case of fentanyl or ketamine [1, 2, 3, 4, 5]. There are only two publications describing propofol abuse, and in both cases propofol was abused for its sedative and relaxing properties [6, 7]. Other possible motives for propofol abuse are sexual illusions and disinhibitions while awakening from the narcotic-induced sleep [8]. In a clinical trial, 40% of patients (N = 546) described pleasurable feelings on awakening [9]. The risk of death due to a self-administered propofol intoxication is very low, primarily due to the low concentration found in commercial ampoules (20 ml containing 200 mg propofol). This is equivalent to a standard dose of 2–2.5 mg/kg body weight for the induction of general anaesthesia within 1–2 min after injection and arousal after 5–10 min. The fast-acting narcotic effect of propofol prevents the self-injection of more than one ampoule at one time. An accumulation of brain propofol levels due to repeated injection after every arousal, i.e. after 20–30 min, cannot be observed because of the fast redistribution from the brain. The pharmacokinetics of propofol can be described by a three-compartment model with a half-life ($t_{1/2}$) of 1.8–8.3 min for distribution, a $t_{1/2}$ β_1 of 34–64 min and a $t_{1/2}\beta_2$ of 184–382 min. The lattermost corresponds to the elimination from adipose tissue [10], but is insignificant due to the rapid metabolism of propofol. Propofol is mainly metabolised by two pathways: either direct glucuronide conjugation or p-hydroxylation with subsequent glucuronidation (or sulphation) [11] where quinol glucuronide amounts to 20–50% of the dose [12]. Only very small amounts are eliminated without being metabolised [10, 11].

We report the case of a death of a male nurse where the situation at the scene indicated a propofol overdose-related death. Doubts existed regarding the self-administration of such high doses of propofol, given knowledge of the pharmacological data. For this reason, analyses were carried out to clarify the situation.

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Case report

A 26-year-old male nurse was found dead in his flat at 8.00 a.m surrounded by several partly empty or unused ampoules of propofol and two syringes. Drug packs of diphenhydramine, amitriptyline, amoxicilline, and ranitidine were also found. His partner reported that the deceased had abused propofol for many years. He was also known to abuse other drugs available to him in the intensive care unit where he worked. He was said to have suffered an acute kidney failure 3 years prior to his death, due to intravenous drug abuse. During the previous 6 months he had been on sick-leave for medical treatment of a depressive illness and to the knowledge of his friend had not abused propofol during the therapy period. He had returned to work 10 days previously and there was no evidence that he intended to take his own life. The nurse and his friend had had a telephone conversation at 4.00 p.m. on the day before his death and had made an appointment for the following day.

Postmortem findings

Due to the findings of rigor mortis and livores at 8.00 a.m., death was estimated to have occurred the previous evening. The weight of the deceased was 91 kg, the lungs and brain were oedematous and congested, but the heart, coronary vessels, aorta and kidneys showed no pathological changes. The organ weights were brain 1520 g, heart 385 g, lungs 1780 g, kidneys 310 g, liver 2170 g, spleen 265 g, and the bladder contained approx. 250 ml urine. Needle marks were found on the forearm, inside of the elbows, wrist, and back of the hand and were fresh or partially scarred. In the areas where the shin-bone made contact with the ground, skin vesicles were found. Furthermore, an aspiration of stomach contents was found during autopsy. Using routine H&E staining, the only histopathological finding was a fatty liver.

Materials and methods

Pure propofol was kindly donated by Zeneca, thymol used as the internal standard was obtained from Fluka and all other chemicals and reagents were of analytical grade and used as purchased.

A systematic toxicological analysis was carried out and the urine sample was screened for drugs and drugs of abuse by immunoassay using the CEDIA, Hitachi 911-Analyser (Boehringer Mannheim, Germany), and FPIA (ADx-System, Abbott, Wiesbaden, Germany) according to the manufacturer's instructions. Further general unknown screening for acid, neutral and basic drugs was performed after alkaline or acid liquid–liquid or SPE extraction by TLC [13], GC, GC/MS [14], and HPLC [15].

Determination of propofol

Solid tissue samples were minced and 1 g was homogenized with two parts of water and ultrasonicated for 30 min, then centrifuged. Blood samples were only centrifuged. Urine was analysed untreated and acid hydrolysed at 100 °C for 30 min. The supernatants of the tissue samples, blood, and (neutralised) urine samples were spiked with thymol and subsequently diluted with one volume of K_2HPO_4 buffer (1.5 mol/l, pH 6.8). The samples were extracted twice with 3 ml cyclohexane, ethanolic NaOH (100 µl 0.1 mol/l in ethanol) was added to the organic phase and the extract was dried at 40 °C under a slow stream of nitrogen. The samples were reconstituted with 50 µl ethanol and 1 µl was injected (splitless mode) into a Hewlett Packard (HP) gas chromatograph 5890 series II coupled to a HP 5972 mass selective detector. Helium was used as carrier gas with a flow rate of 1 ml/min. A (5%) phenyl-methylpolysiloxane capillary column (HP-5MS, 30 m × 0.25 mm internal diameter, 0.25 µm film thickness) was used for separation. Operating temperatures for injector and detector were 200 °C and 280 °C, respectively. The oven temperature was programmed from 100 °C (1 min hold) to 240 °C at 20 °C/min (5 min hold) and to 280 °C at 10 °C/min (20 min hold). The mass spectrometer was operated in EI mode and in a full-scan mode.

Since hair material was very limited in this case, it was not possible to perform a special method for determining propofol in hair. Instead, our routine method for general unknown hair analysis was used to screen for a broad spectrum of substances. Hair samples were taken by cutting the hair as close to the scalp as possible and, starting at the scalp (0), were cut into segments of 2 cm, washed three times (aqua dest, acetone, CH_2Cl_2), and dried. The segments were pulverized separately in a ball mill, and 2 ml methanol and 200 ng of the internal standard methaqualone were added to 50 mg of the pulverized hair. This mixture was put in an ultrasonic bath for 4 h. After centrifugation the supernatant was transferred to a clean vessel and 2 ml methanol was added to the residue and again ultrasonicated for 4 h. After centrifugation the two supernatants were combined, ethanolic NaOH (100 µl) was added and evaporated to dryness under a stream of nitrogen at 40 °C. The reconstituted samples were examined by GC/MS using the same methods as for the body fluids.

Calibration curve

Standard 6-point calibration curves were obtained using 0.01 µg–10 µg propofol/ml serum blank and for hair using 0.01–0.5 µg propofol/50 mg hair blank. The detection limit was determined according to DIN 32645 [16] to be 0.04 µg propofol/ml serum and for hair 0.2 µg propofol/g using 50 mg hair. The calibration curves were found to be linear over the whole calibration range. The recovery for spiked serum samples was determined to be 65% at 0.1 µg/ml and 64% at 3 µg/ml. Precision results showed an intra-assay variance of propofol determination in serum (n = 6) of 4.7% (at 0.1 µg/ml) and 4.3% (at 3 µg/ml). Inter-assay variance determined on five different days was 6.9% (at 0.1 µg/ml) and 6.7% (at 3 µg/ml). The recovery for spiked minced liver samples was determined to be 65% at 3 µg/ml and 54% for hair at 0.1 µg propofol/g.

Results

The toxicological examination revealed the presence of propofol and diphenhydramine, but other pharmacologically relevant substances or alcohol were not detected. The blood concentration of diphenhydramine was negligible (0.09 µg/ml) and the analytical results of propofol determination in blood, urine and various organs are summarised in Table 1. Propofol was mainly metabolised by two pathways: either direct glucuronide conjugation or p-hydroxylation with subsequent glucuronidation (or sulphation). Only very small amounts were eliminated without metabolisation. Acidic urine hydrolysis increased the propofol concentration from 5.4 µg/ml to 8900 µg/ml. Because the bladder contained 250 ml urine, the amount of propofol eliminated was found to be 2225 mg. This does not take the other hydroxy metabolites into account for which a quantitation was not possible due to the absence of standards. Therefore more than 11 ampoules of 20 ml propofol emulsion must have been administered during the last hours before death.

Hydrolysis of quinol conjugates in urine yielded 2,6-diisopropyl-1,4-quinone due to the fast oxidation of the liberated quinol aglycone. Even without hydrolysis smaller amounts of the oxidised metabolites could be detected in all body fluids, tissues, and even in hair. Quantitation of propo-

Table 1 Results of toxicological analyses compared with two other fatal cases of propofol overdose (2,6-diisopropyl-1,4-quinol and 2,6-diisopropyl-1,4-quinone were found in all our samples). *n.d.* not determined

	This case		Fatality 1 [17] Propofol (μg/g)	Fatality 2 [18] Propofol (μg/g)
	Propofol (μg/g)	Diphenhydramine (μg/g)		
Blood	5.3	0.09	0.22	2.5
Cerebellum	7.6	n.d.	n.d.	n.d.
Medulla oblongata	8.1	n.d.	n.d.	11.3 (brain)
Urine	5.4	0.1	5.4	n.d.
Urine hydrolysed	8900	n.d.	94	n.d.
Liver	27	0.13	1.4	22
Hair segment 0–2 cm	3.5	Trace	n.d.	n.d.
Hair segment 2–4 cm	1.4	Trace	n.d.	n.d.
Hair segment 4–6 cm	1.05	Trace	n.d.	n.d.

fol in three different hair segments showed an increase in the concentrations towards the proximal (scalp) end.

Discussion

In order to assess the relevance of the propofol blood concentrations measured in this case, they were compared to two fatal cases of propofol abuse reported in literature (Table 1). The first case concerned a female radiographer who was thought to have abused propofol for a prolonged period of time [17]. The other case was the suicide of a medical doctor who used two hypodermic needles to infuse propanol into the back of the hand [18]. The propofol blood concentrations in our case were greater than those found in these cases by a factor of 24 and 2, respectively. These concentrations as well as the high level of propofol found in the urine demonstrate the high dose used by the male nurse. It is generally considered that such a high concentration of propofol cannot be self-administered, resulting, at first glance, in the conclusion that it must have been administered by a third party. However, taking all the facts of the case into account this conclusion cannot be sustained.

After a bolus injection, patients lose consciousness at propofol blood concentrations of 1.3–6.8 μg/ml and regain consciousness after 8–10 min at concentrations of 1–2.5 μg/ml [19, 20, 21, 22, 23]. Thus the propofol blood concentration of 5.3 μg/ml measured in our case is well within the concentration range for anaesthesia, leading to the conclusion that death could have occurred immediately following the propofol injection. In the case of the radiographer a longer survival time has to be assumed, whereas in the case of the medical doctor the possibility of different pharmacokinetics due to the absence of a bolus injection has to be taken into account. Thus the high brain concentration compared to the plasma concentration would represent the equilibrium distribution between brain and blood. There is a sharp decline in propofol brain concentrations due to the redistribution from the central compartment (which includes the CNS) into peripheral compartments, resulting in an awakening of the patient from the anaesthetic. Even during the disposition phase the rapid breakdown of propofol results in a steep decline of the propofol blood concentration. The extremely high urine concentration (hydrolysed urine: 8900 μg propofol/ml) in our case has to be taken as a sign of this elimination. At autopsy the bladder contained approx. 250 ml. Assuming a urine production of 40–50 ml/h the bladder contents would have been produced within 6 h and therefore there would have been at least 12 injections of one ampoule each within this time period. Using a $t_{1/2}\beta$ of 30 min, a distribution volume of 2 l/kg and the assumption of being able to inject one ampoule every 30 min there would have been a blood propofol concentration of 1–2 μg/ml at the time of the last injection. Such a high frequency of injections within the last 6 h makes it necessary to take cumulative effects of the propofol blood concentration into account. Due to the fast redistribution this accumulation is of no significance for CNS effects. Therefore the blood concentration resulting from the last injection has to be reduced by 1–2 μg/ml.

In our case the cause of death would not be a multiple overdose but an accidental complication caused, for example, by apnoea or a drop in blood pressure. Hypotension and apnoea are relevant side effects [24] which also occur with other anaesthetic agents [25] and are probably dependent on the dose and speed of propofol administration. Apnoea during anaesthesia induction occurs more frequently with propofol than with other anaesthetics and the duration is usually short but can persist for up to 3 min [24]. Several fatalities have been reported after continuous propofol infusion or sedation in children [26, 27], and some authors have linked propofol to induction of malignant hyperthermia in children. Other fatalities after anaesthetic propofol induction have been reported from high-risk patients who suffered a cardiovascular collapse [28].

Taking this evidence as well as the normal redistribution phase of propofol blood levels into account, it is more probable that death was caused by an overly rapid injection of a normal propofol dose than by a propofol overdose.

Propofol as a substance of abuse

It is well known that the results of hair analysis have to be assessed with care [29, 30, 31]. By analysing hair segments

we could prove that the propofol abuse of the male nurse was not a single excessive dose but an increasing chronic abuse.

A similar pattern of excessive abuse was evident in the case of an anaesthesiologist who first abused and was then addicted to propofol for about 1 year, whereby it was not the amount per injection that was increased (always 100 mg) but the frequency (up to 15 times per day) [6]. A different pattern of abuse was found in a rehabilitated alcoholic who abused propofol three times a day with doses of 50 mg for 9 days [7].

Due to the short duration of the narcotic effect, propofol abuse is very easy to conceal. This very rare case of a documented chronic propofol abuse in combination with the excessive frequency of administration just before death demonstrates that hospital personnel may show patterns of misuse different from those of normal addicts.

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