Death after excessive propofol abuse

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Abstract

Abuse of the anaesthetic agent propofol (2,6-diisopropylphenol) is rare. We report a case of a 26-year-old male nurse in which autopsy showed unspecific signs of intoxication. Criminological evidence pointed towards propofol abuse and/or overdose. Intravenously administered propofol is a fast as well as short acting narcotic agent. Therefore it seemed questionable whether the deceased was able to self-administer a lethal overdose before loosing consciousness. The blood and brain concentrations corresponded to the concentrations found 1-2min after bolus administration of a narcotic standard dose of 2.5mg propofol/kg body weight. Extremely high propofol concentrations were found in urine indicating multiple abuse before death. Due to the short half-life of propofol the cumulative toxic effect of repeated injections should not be relevant for toxicity since this would result in a blood level increase of only 1-2$\mu g/ml$. The detection and quantitation of propofol in three different hair segments indicates a chronic propofol abuse of the deceased. The results of the investigation suggest that death was not caused by a propfol overdose but by respiratory depression resulting from too fast an injection.

Keywords

Chronic propofol abuse, Toxicology, Fatal propofol overdose, Hair analysis, Brain concentration

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1 Introduction

Propofol is a new short-acting anaesthetic used for inducting and maintaining general anaestesia. It has no affinity to opiate-, benzodiazepin-, or NDMA-receptors and thus should have no potential for abuse or addication—which are always associated with the risk of overdosing like Fentanyl or Ketamine [1, 2, 3, 4, 5]. There are only two publications describing propofol abuse. In both cases propofol was used for its sedative and relaxing property [6, 7]. Other possible motives for propofol abuse are sexual illusions and disinhibitions during awakening from the narcotic-induced sleep [8]. In a clinical trail 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, the main reason being the low concentration found in commercial ampoules (20ml containing 200mg propofol). This amounts to a standard dose of 2-2.5mg/kg body weight for the induction of a general anaesthesia within 1-2min after injection and an arousal after 5-10min. The fast acting narcotic effect of propofol prevents the self-injection of more than one ampoule at a time. A cumulation of brain propofol levels due to repeated injection just after arousal, i.e. after 20-30min, cannot be observed because of the fast redistribution from the brain. The pharmacokinetic of propofol can be described by a three compartment model with a $t_{1/2}$ of 1.8-8.3min for distribution, $t_{1/2}\beta_1$ of 34-64min and $t_{1/2}\beta_2$ of 184-382min. The last half-life corresponds to the elimination from adipose tissue [10], but being insignificant due to the rapid metabolism of propofol. Propofol is maily metabolised by two pathways: either direct glucronide 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 aliminated without being metabolised [10, 11].

We report on the death of a male nurse found dead in his flat with several empty propofol ampoules littering the floor. His partner said he knew about a propofol abuse for several years though non was abused during the last couple of months. Doupts existed regarding the self-administration of such high doses of propofol knowing the pharmacological data. Therefore analyses were made to clarify this case.

2 Case report

A 26-year-old male nurse was found dead in his flat at 8am. He was surrounded by several partly empty as well as unused ampoules of propofol and two syringes. Furthermore drug packs of diphenhydramine, amitriptyline, amoxicilline, and ranitidine were 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 at work. He was said to have suffered an acute kidney failure 3 years ago which was said to be due to his intravenous drug abuse. During the previous 6 months he was on sick-leave for medical treatment of his depressive illness. To the knowledge of his friend he did not abuse propofol during therapy. Ten days before his death he returned to work. There was no evidence that he intended to take his own life. The nurse and his friend had a telephone conversation at 4 p.m. on the day before his death when they made an appointment for the following day.

2.1 Post-mortem

Due to the findings of rigor mortis and livores at 8 a.m. death was attributed to have occurred the previous evening. The weight of the deceased was 91kg. Lung and brain were oedematous and congested. The heart, coronary vessels, aorta, and kidney did not show any pathological changes. The organ weights were: brain 1520g, heart 385g, lungs 1780g, kidneys 310g, liver 2170g, spleen 265g. The bladder contained approx. 250ml urine. Needle marks were found on the forearm, inside of his elbows, wrist, and back of the hand, they were fresh or partially scarred. In the areas were the shin-bone touched the ground skin vesicles were found. Furthermore an aspiration of stomach contents was diagnosed during autopsy. Using the routine HE staining the only histopathological finding was a fatty liver.

3 Materials and methods

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

3.1 Systematic toxicological analysis

Urine samples were screened for drugs and drugs of abuse by immunoassays using the CEDIA, Hitachi 911-Analyser (Boehringer Mannheim Mannheim, Germany), Hitachi, 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].

3.2 Determination of propofol

Solid tissue samples were minced and 1g was homogenized with two parts of water and ultrasonicated for 30min, then centrifuged. Blood samples were only centrifuged. Urine was analyzed untreated and acidic hydrolyzed at 100°C for 30min. The supernatants of the tissue samples, blood, and (neutralised) urine samples were spiked with thymol and subsequently diluted with one volume of KH_2PO_4 buffer (1.5mol/l, pH 6.8, one part saturated KH_2PO_4 solution, 3 parts aqua dest.). The samples were extracted twice with 3ml cyclohexane. Ethanolic $NaOH$ (100μl, 0.1mol/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 50μl ethanol and 1μl 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 1ml/min. A (5% phenyl)-methylpolysiloxane capillary column (HP-5MS, 30m × 0.25mm internal diameter, 0.25μm 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 (1min hold) to

240°C at 20°C/min (5min hold) and to 280°C at 10°C/min (20min hold). The mass spectrometer was operated in EI mode and in full-scan mode.
Since the amount of hair material was limited in this case no special method for propofol determination in hair was developed. 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. Starting at the scalp (0cm) they were cut into segments of 2cm, washed three times (aqua dest., acetone, CH_2Cl_2), and dried. Afterwards the segments were separately pulverized using a ball mill. 2ml methanol and 200ng of the internal standard methaqualon were added to 50mg of the pulverized hair. This mixture was incubated in an ultrasonic bath for 4h. After centrifugation the supernatant was transferred to a clean vessel and 2ml methanol was added to the residue and again incubated for 4 hours. After centrifugation the two supernatants were combined, ethanolic $NaOH$ (100μl) was added and evaporated to dryness under a stream of nitrogen at 40°C. The reconstituted samples were examined by GC/MS using the proven methods aused for the body fluids.

3.3 Calibration curve

Standard 6-point calibration curves were obtained using 0.01–10μg propofol/ml serum blank and for hair using 0.01μg - 0.5μg propofol/50mg hair blank. The detection limit was determined according to DIN 32645 [16]. It was 0.04μg propofol/ml serum and 0.2μg propofol/g using 50mg 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$\mu g/ml$ and 64% at 3$\mu g/ml$. Precision results showed an intraassay variance of propofol determination in serum (n = 6) of 4.7% (at 0.1$\mu g/ml$) and 4.3% (at 3$\mu g/ml$). Inter-assay variance determined on 5 different days was 6.9% (at 0.1$\mu g/ml$) and 6.7% (at 3$\mu g/ml$). The recovery for spiked minced liver samples was determined to be 65% at 3$\mu g/ml$ and 54% for hair at 0.1μg propofol/g.

4 Results

The toxicological examination revealed the presence of propofol and diphenhydramine. Other pharmacological relevant substances or alcohol were not detected. The blood concentration of diphenhydramine was neglectable (0.09$\mu g/ml$). Analytical results of propofol determination in blood, urine, and various organs are summarised in Table 1. Propofol was mainly metabolized by two pathways: either direct glucuronide conjugation or p-hydroxylation with subsequent glucuronidation (or sulphation) [11]. Only very small amounts were eliminated without metabolization [10, 11]. Acidic urine hydrolysis increased the propofol concentration from 5.4$\mu g/ml$ to 8900$\mu g/ml$. Because the urine bladder contained 250ml urine the eliminated propofol amounted to 2225mg even without the other hydroxy metabolites for which the quantification was made impossible by the lack of standards. Therefore more than 11 ampoules of 20ml propofol emulsion must have been administered during the last hours before death.

	This Case		Case 1 [16]	Case 2 [12]
	Propofol [$\mu g/ml$]	Diphenhydramine [$\mu g/ml$]	Propofol [$\mu g/ml$]	Propofol [$\mu g/ml$]
Blood	5.3	0.09	0.22	2.5
Brain				11.3
Medulla	8.1	n.d.	n.d.	
Cerebellum	7.6	n.d.	n.d.	n.d.
Urine	5.4	0.1	5.4	n.d.
hydrol.	8900	n.d.	94	n.d.
Liver	27	0.13	1.4	22
Hair segment				
0-2cm	3.5	trace	n.d.	n.d.
2-4cm	1.4	trace	n.d.	n.d.
4-6cm	1.05	trace	n.d.	n.d.

n.d. not determined

Table 1: Results of toxicological analysis 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.)

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 oxidized metabolites could be detected in all body fluids, tissues, and even in hair. Due to the absence of standards for the quinol and other unidentified metabolites a quantification of the metabolites was not possible. According to Vree et.al. [12] the quinol glucuronide amounts to 20-50% of the dose.
Quantification of propofol in 3 different hair segments showed an increase in the concentrations towards the scalp i.e. the proximal end.

5 Discussion

In order to assess the relevancy of the measured propofol blood concentrations of this case they were compared to two fatal cases of propofol abuse reported in literature (Tab. 1). The first case concerned a female radiographer who was said to have abused propofol for a prolonged period of time [17]. The other case regards the suicide of a medical doctor who used two hypodermic needles in the back of his hand for an infusion of propofol [18]. The propofol blood concentrations in our case were higher by a factor of 24 and 2, respectively. These concentrations as well as the high level of propofol found in the brain tissue demonstrates how high the concentrations used by the male nurse really were. It is commonly said that such high a concentration of propofol can not be self-administered, resulting—at the first glance—in the conclusion that it had to be administered by a third party. However, taking all the facts of the case into account this conclusion can not be maintained.

After a bolus injection consciousness is lost in patients at propofol blood concentrations of 1.3-6.8$\mu g/ml$. Consciousness was regained after 8-10min at concentrations of 1-2.5$\mu g/ml$ [19, 20, 21, 22, 23]. Thus the propofol blood concentration of 5.3$\mu g/ml$ measured in our case is well within the range of the anaesthetically used concentrations during the institution of a narcosis, leading to the conclusion that death could have occured immediatly 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 with regard 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: 8900μg propofol$/ml$) in our case has to be taken as a sign of this elimination. At autopsy the bladder contained approx. 250ml. Assuming a urine production of 40-50ml/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 $t_{1/2}$ of 30min, a distribution volume of 2l/kg and the assumption of being able to inject one ampoule every 30min there would have been a blood propofol concentration of 1-2$\mu g/ml$ at the time of the last injection. Such a high frequency of injections within the last 6h 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$\mu g/ml$.

In our case the cause of death would not be a multiple overdose but an accidental complication caused e.g. by apnoe or a drop in blood-pressure [24, 25]. Complications due to dysfunction of the kidneys as a result of the anuric state of 3 years ago has been ruled out by histological examination as well as the fact that propofol is eliminated by hepatic metabolism.

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. The apnoea duration is usually short but it can persist for up to 3 minutes [24]. Several fatalities were reported after continuous propofol infusion or sedation in children [26, 27]. Some authors link propofol to malignant hyperthermia induction in children. Other fatalities after anaesthesiological propofol induction were reported from high risk patients who suffered cardiovascular collapse [28].

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

6 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 an excessive one-off abuse but an increasing cronic one. A similar pattern of excessive abuse was evident in the case of an anaesthesiologist who first abused and then was addicted to propofol for about a year. He did not increase the amount per injection (always 100mg) but the frequency (up to 15 times per day) [6]. A different pattern of abuse was found in a sober alcoholic who abused propofol 3 times a day with doses of 50mg for nine days [7].
Due to the short duration of the narcotic effect propofol abuse is especially easy to hide. 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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