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Deaths from recreational use of propofol in Korea

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ABSTRACT

Propofol, a short-acting and sedative-hypnotic agent, induces and maintains anesthesia. Since it is known to produce mild euphoria and hallucinations, the recreational use of propofol has been a big issue in Korea. Furthermore, many deaths have occurred due to its abuse and misuse. In order to study the prevalence of abuse and deaths due to propofol, all autopsy cases conducted between 2005 and 2010 at the NFS (National Forensic Service, Korea) were monitored by checking its concentrations in the blood. Propofol was detected in 131 cases (0.88%) out of 14,673 autopsied cases within 6 years. Propofol alone was detected in 49 of 131 fatal cases, while the combination of drugs was detected with propofol in the remaining 82 cases.

The concentrations of propofol from autopsied cases ranged from 0.05 to 8.83 mg/L (mean 1.66; median 0.9) and from 0.08 to 8.65 mg/L (mean 1.71; median 1.05) in the heart ($n = 31$) and the femoral blood ($n = 32$), respectively. The investigation of the ratio of heart to femoral blood and the difference between the concentrations in heart and femoral blood ($n = 15$) from the same body revealed the ratio from 0.45 to 3.66 (mean 1.53; median 1.40).

The autopsy resulted in accidental death after self-administration in 16 autopsied cases among 131 autopsied cases. In 16 cases, their ages ranged from 17 to 56 and 75% of them were in their 20's and 30's and 75% were female. Half of them were medical personnel including 19% of doctors and 38% of nurses. The combination of drugs was detected in 6 cases. Fluoxetine was detected in three and vecuronium was detected in two along with propofol. The cause of death in 14 cases was drug intoxication, while that in 2 cases was hanging.

Due to its prevalence, Korea has become the first country that regulates propofol as a psychotropic substance.

1. Introduction

Propofol (2,6-diisopropylphenol) is a short-acting and sedative-hypnotic agent that induces and maintains anesthesia [1,2]. Due to its rapid recovery and a faster onset of action, general physicians and surgeons prefer to use it instead of other anesthesia [3–5,2,6,7]. However there are several side effects including low blood pressure, bradycardia, hypotension, cardiac arrhythmia, transient apnea, dystonia, and mild myoclonic movements [8–10]. Since its side effects contain euphoria, sexual hallucinations and disinhibition during recovery, people are inclined to use it for recreational purposes [11–14]. In fact, the recreational use of propofol has been a big issue in Korea. Because many plastic surgery clinics often use it, some female clients have become addicted due to undergoing frequent plastic surgeries. There is also an assumption that Korean entertainers abuse propofol because they believe the drug is good for stress and insomnia. In addition, some doctors in local clinics have sold propofol shots as packages grouped with massages under false pretenses. Now, the government could take measures against these practices by the law. Roussin et al. [11] reported evidence of the potential for abuse and dependence on propofol. Zacny et al. [15] concluded that propofol may be rewarding (reinforcing) in some individuals without a history of drug abuse. Wilson et al. [1] recommended that the U.S. Drug Enforcement Administration and other international agencies should consider regulating propofol as a controlled substance.

Because its abuse had been prevalent among celebrities as well as housewives, the Korean government classified it as a psychotropic agent in 2011 and regulated its use. Korea has become the first country that regulates propofol as a psychotropic substance. Even though it has been controlled, its abuse continues. In 2013, three famous female celebrities were charged with its

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illegal use. According to a report by the prosecution, they took propofol between 95 to 185 times. But they claimed that they used it for medical purposes, not to help them sleep or for recreational use. However, because the safety margin of propofol is very narrow, deaths have occurred accidentally in many cases, just as it contributed to the death of pop star Michael Jackson. Propofol is especially highly abused by medical professionals including nurses, nurse's aides and medical doctors [11,16–18]. In this study, in order to observe the prevalence of propofol abuse, all autopsy cases conducted between 2005 and 2010 at the NFS (National Forensic Service, Korea) were monitored by checking its concentration in the blood. Firstly, a method was validated and then applied to determine the concentration. In all cases, systematic screening was conducted to detect propofol as well as other drugs. Among propofol positive cases, the blood concentrations in the femoral and the heart blood were evaluated to study the postmortem redistribution (PR). The autopsy resulted in accidental death after self-administration in 16 autopsied cases among 131 autopsied cases. The occupation, age, gender, case study, and detection of other drugs were investigated to determine the causes of deaths.

2. Methods

2.1. Chemicals

Propofol (2,6-diisopropylphenol), 99.8% purity, was obtained from Cerilliant (TX, USA). Thymol (2-isopropyl-5-methylphenol), 99.5% purity, disodium hydrogen phosphate and monosodium phosphate were purchased from Sigma-Aldrich (MO, USA). HPLC grade methanol, chloroform and ethyl acetate, sodium hydroxide and sodium sulfate were obtained from Merck (Darmstadt, Germany).

2.2. Standard and internal standard solutions and calibration standards

Stock solutions (1 mg/mL) of propofol and internal standard, thymol, were prepared in methanol and stored at −20 °C. Standard solutions were made by further dilution of stock solutions with methanol. For calibration curves, drug-free whole blood samples obtained from the deceased (1 mL) were spiked with diluted standard solutions to give final concentrations of 0.05, 0.075, 0.1, 0.125, 0.15, 0.5, 1, 1.5 and 2 mg/L.

2.3. Sample collection

After autopsy, blood samples were collected and analyzed. Post-mortem cardiac and femoral blood specimens were collected in 50 mL plastic tubes and stored at 4 °C until analysis. The average time between the arrival of the body at NFS and the sample collection was approximately 3 h. Every year over 2000 autopsies were performed at the headquarters of NFS and a total of 14,673 autopsied cases were studied.

2.4. Sample preparation

One mL of whole blood sample (done in triplicate) was put into a 15-mL glass screw cap tube to which the following was added: 50 μL of thymol (10 mg/L) as an internal standard, 0.5 mL of 0.05 M phosphate buffer (pH 6.0) and 0.2 mL of 0.1 M sodium hydroxide. Then 5 mL of chloroform–ethylacetate (70:30, v/v) was added, and the analytes were extracted gently by mechanical shaking for 30 min at 50 rpm. After centrifugation, an aliquot of the organic layer (bottom) was transferred to a glass tube containing sodium sulfate to eliminate water and was evaporated to dryness under nitrogen for 15 min. The dried extract was reconstituted in 100 μL of methanol. One μL was injected into the capillary column of the GC–MS system.

2.5. GC/MS system

The GC–MS system consisted of a Hewlett Packard 7683 series injector, HP 6890 series GC system (Wilmington, DE, USA), and HP 5973 mass selective detector. The column used (Agilent Technologies, Foster, CA, USA) was a fused silica capillary column (HP-5 MS capillary column, 30.0 m × 250 μm × 0.25 μm). The injector was operated in the splitless mode, the injection volume was 1 μL, the injector temperature was 200 °C, the ionization energy was 70 eV and the transfer line temperature was 280 °C. Initial oven temperature was 50 °C, maintained for 1 min, increasing at 10 °C/min to 190 °C and increasing at 20 °C/min to 290 °C. GC/MS was operated in selected ion monitoring mode (SIM). The quantification of propofol was based on peak area ratios. The m/z and retention time of propofol and thymol (internal standard) were as follows: propofol, m/z 163, 178, 121, RT 11.82 min; thymol, m/z 135, 150, 91, RT 10.86 min (the underlined ions were used for quantitation).

2.6. Method validation

The method was validated by establishing specificity, selectivity, limit of detection (LOD), limit of quantification (LOQ), linearity, intra- and inter-assay accuracy, precision and recovery. To evaluate selectivity, fifty-five frequently detected drugs including amitriptyline, benztropine, etc. were added to six drug-free whole blood samples at concentrations of 0.1 mg/L for checking the interference. The LOQ was evaluated in triplicate and defined as the concentration that met LOD criteria for which the signal-to-noise ratio was at least 10:1 and the measured concentration was within 20% of the target in three replicates. Nine calibration standards ranging in concentrations from 0.05 to 2 mg/L propofol were prepared using 1 mL of drug-free blood. Spiked drug-free blood samples (1 mL) containing low, medium and high concentrations of propofol (0.08, 0.2 and 0.8 mg/L) were prepared in order to assess intra-assay ($n = 6$) accuracy and precision. The inter-assay ($n = 18$) accuracy and precision were also examined in series on five consecutive days. Recovery was determined at 0.08, 0.2 and 0.8 mg/L of propofol and peak area ratios of propofol to thymol were compared with those of methanolic standards.

3. Results

3.1. Validation of the method

Table 1 shows the results of the method validation for propofol in blood. For specificity and selectivity, all six whole blood samples were free of co-eluting peaks at the retention times of propofol and thymol. The 55 commonly encountered medicines, which were added at 0.1 mg/L, did not interfere with propofol quantitation (0.2 mg/L) resulting in accuracy of +4.28% and a precision of 6.65%. The LOD and LOQ of propofol using 1 mL of blood were 0.02 and 0.05 mg/L, respectively. The calibration curves for propofol were linear in the concentration range of 0.05–2 mg/L and R^2 was 0.9931. The intra- ($n = 6$) and inter-assay ($n = 18$) inaccuracy and imprecision for propofol in whole blood were all less than 14.04% at three concentrations. The recoveries of medium and high concentration groups were high, but that of the low concentration group was low. Overall, recoveries ranged from 82% to 116%.

3.2. Prevalence of propofol abuse

Among a total of 14,673 autopsies, propofol was detected in 131 cases. As shown in Fig. 1, it was detected in 5 cases in 2005, 21 in 2006, 18 in 2007, 21 in 2008, 33 in 2009 and 33 in 2010. Among them, there were cases in which the combination of other drugs

Table 1
Validation data of propofol in whole blood.

Analyte (mg/L)	Accuracy[a] (%bias)		Precision[b] (%CV)		Recovery (%)
	Intra-day ($n = 6$)	Inter-day ($n = 18$)	Intra-day ($n = 6$)	Inter-day ($n = 18$)	$n = 6$
0.08	10.59	11.67	14.08	14.00	82
0.2	10.62	14.04	4.36	9.83	116
0.8	−13.39	9.50	10.32	13.56	105

[a] Calculated as [(mean calculated concentration − nominal concentration)/nominal concentration] × 100 (% bias).
[b] The coefficient of variation (% CV): SD/mean × 100%.
*Limit of detection: 0.02 mg/L (using 1 mL of blood).
*Limit of quantitation: 0.05 mg/L (using 1 mL of blood).