Original article:

Abstract

For a better understanding of circumstantial and toxicological findings of fatalities resulting from self-administration of intravenous anesthetic/narcotic agents, medico-legal autopsy files of the State Institute of Legal and Social Medicine Berlin during 1998-2011 was reviewed retrospectively. Of a total of 15,300 autopsies, 9 cases of such deaths were identified and all were health care professionals. Medical supplies for injection were found still on or near the body at the scene. Anesthetic/narcotic agents detected were classified into 3 categories, and administered solely or in combination. Propofol was detected in 6 cases and the most common agent. In 2 out of 6 cases, propofol was detected at heavily over-therapeutic levels causing death. In remaining 4 cases, propofol levels were within therapeutic range, but propofol intoxication was considered as lethality by rapid continuous injection. In 5 cases, injection of opioid narcotics was fatal. Alongside the 2 propofol-detected cases, there was one case where a higher-than-therapeutic level of piritramide and a therapeutic level of alfentanil. Despite suspected its usage, remifentanil was undetected due to rapid metabolization by elastases in one case and sufentanil was undetectable due to putrefaction in another, but death was attributed to being caused by their potent respiratory depressant effects without respiratory assistance. Benzodiazepines were detected in 4 cases. All of them were used together with propofol or opioids, and contributed to death by inhibiting respiration. It is essential to consider means of administration as well as **additive or synergistic** effects of combined agents when interpreting toxicological results in these cases.

Key words

intravenous anesthetic/narcotic agents; self-administration; health care professionals; propofol; therapeutic level; respiratory depressant effects

Introduction

Intravenous anesthetic/narcotic agents such as barbiturates, benzodiazepines, ketamine, etomidate, propofol and opioid analogues cause reversible loss of consciousness and sensation during anesthesia by depressing the central nervous system [1]. Not all too long ago there was a propofol-related death which generated tremendous publicity - the death of the world-renowned musician, Michael Jackson. In medico-legal autopsy practice, fatalities caused by these substances are rare compared with other poisoning deaths. Such deaths are most frequently due to self-administration of intravenous anesthetic/narcotic agents. These fatalities are limited to specific occupations as both the acquisition and administration of the agents used are distinctive. Deaths resulting from self-administration of said agents - such as fentanyl [2-8], midazolam [9-11] or propofol [12-21] - have been reported sporadically in the literature. This has meant a predominantly analytical rather than systematic approach to this topic. The present retrospective study has been conducted to better characterize the phenomenology as well as toxicology of fatalities occurring from self-administered intravenous anesthetic/narcotic agents.

Materials and Methods

Case selection

A retrospective review of the 1998-2011 medico-legal autopsy files (*n*=15,300) of the State Institute of Legal and Social Medicine Berlin - located in Berlin, Germany - was performed for fatalities related to self-administration of intravenous anesthetic/narcotic agents (such as barbiturates, benzodiazepines, ketamine, etomidate, propofol and opioid analogues).

Toxicological analysis

The following substances were used for quantitative analyses in the present study: propofol, morphine, codeine, tramadol, diazepam, midazolam, amiodarone and mirtazapine (which were purchased by LGC Standards (Wesel, Germany)); 4-methylaminoantipyrine and 4-aminoantipyrine (which were purchased by the European Directorate for the Quality of Medicines (Strasbourg, France)); alfentanil, sufentanil and piritramide (which were donated by Janssen-Cilag (Neuss, Germany)); and remifentanyl (which was donated by Glaxo Smith and Kline (Munich, Germany)). All buffer substances and solvents were provided by Merck (Darmstadt, Germany).

Quantitative analyses of femoral venous blood were performed using high-performance liquid chromatography with diode array detectors (HPLC-DAD). Shimadzu HPLC devices (Shimadzu Europe GmbH, Duisburg, Germany) were used for all of measurements consisting of a pump LC-6A, an autosampler SIL-9A, one of the photodiode array detectors SPDM-6A, SPDM-10A or SPDM-10AVP, a degasser Degasys 1210 (VDS Optilab GmbH, Berlin, Germany) and a computer (standard IBM PC). The diode array detectors were operated by the software CLASS or CLASS-VP. A UV spectra library of toxic compounds containing 2686 substances was available for peak identification [22-24]. The chromatographic separation was performed on a reversed phase HPLC column RP8ec, 5 µm, 250 mm × 4.0 mm (Merck, Darmstadt, Germany) and with an isocratic mobile phase consisting of acetonitrile and 0.1 M phosphate buffer pH 2.3 in (37:63, v/v). The measurements were carried out at room temperature (20–25 °C) and at a flow rate 1 mL/min. 5-(4-Methylphenyl)-5-phenylhydantoin (MPPH) was used as the reference substance for calculation of the relative retention time (RRT).

Results

Of the 15,300 total medico-legal autopsies performed from 1998 - 2011, there were 9 cases (2 females and 7 males) of fatal self-administration of intravenous anesthetic/narcotic agents. All of the deceased were health care professionals (6 medical doctors and 3 nurses). **Their specialties included 4 anesthesiologists, 1 surgeon, 1 general practitioner, 2 Intensive care unit (ICU) nurses and 1 scrub nurse.** Their ages ranged from 26 to 54 years old (an average of 44 years). In all cases except case no. 1, the administered intravenous anesthetic/narcotic agents were clearly obtained from the workplace of the deceased. In all cases medical supplies for intravenous injections such as infusion catheters (4 cases) attached with infusion bottles or syringes (5 cases) were still inserted into the body or found near the body at the scene of death. In all cases autopsies found puncture marks at anatomically viable self-administration sites. Except for one case (case no. 7) where the manner of death remained undetermined, the manner of death was suicide (in 8 cases). In 7 out of 9 cases (except case nos. 7 and 8) various prescriptions including anesthetic/narcotic agents were detected in femoral venous blood of the deceased. In 6 cases (case nos. 1-6) propofol was detected in femoral venous blood. Its concentration ranged from 1.7 to 13 µg/mL. In 5 cases (case nos. 1, 6, 7, 8 and 9) opioids such as fentanyl analogues (alfentanil, remifentanil and sufentanil), morphine, codeine, piritramide and tramadol had been used. Alfentanil was detected in femoral venous blood of

case nos. 1 and 9. The concentrations were 0.1 μg/mL and 0.2 μg/mL respectively. In case no. 7 remifentanil was not detected in the blood. However, an empty ampule of it was found in the deceased's left hand. In case no. 8 no sufentanil could be detected in muscle tissue. Sufentanil, however, was detected in the fluid remaining within the syringes found near the body. In case nos. 6 and 9 piritramide was detected in femoral venous blood with concentrations between 0.01 μg/mL and 0.04 μg/mL respectively. There was only one case (case no. 6) where morphine, codeine and tramadol were detected in the blood. Benzodiazepines such as diazepam and midazolam were detected in femoral venous blood in 4 cases (case nos. 2, 3, 6 and 9). Alongside the anesthetic/narcotic agents, the antiarrhythmic amiodarone, the antidepressant mirtazapine, and the analgesic and antipyretic dipyrone were uniquely detected in the blood in case nos. 4, 5 and 7 respectively. Case no. 1 was the only instance where the deceased was under the influence of ethanol at the time of death. Individual case reports are provided below and the case data listed in Table 1.

Individual case presentations

Case 1

A 48-year-old male **general practitioner** was found dead in his own clinic. There was an infusion catheter inserted into the vein of the left antecubital fossa which was attached to an infusion bottle (500 mL) containing a little milky-colored fluid. The financial difficulty of the clinic was a considerable burden to him, **and he had had previous suicide attempts**. At autopsy a fresh puncture mark was noticed in the left antecubital fossa. The brain and lungs were edematous and congested. Toxicological analysis of femoral venous blood revealed 9.7 μg/mL of propofol and 0.1 μg/mL of alfentanil. Femoral venous blood and urine ethanol concentrations were 1.2 mg/mL and 1.6 mg/mL respectively. The cause of death was attributed to a self-administered overdose of propofol and a therapeutic dose of alfentanil with ethanol. The manner of death was determined to be suicide.

Case 2

A 46-year-old male **anesthesiologist** was found dead in his apartment. There was an infusion catheter which was attached with an infusion bottle (500 mL) containing approximately 10 mL of a milky-colored fluid, inserted into the vein of the left antecubital fossa. There was a suicide note which indicated that the man had committed suicide due to grieving for the death of his partner. Autopsy revealed a fresh puncture mark in the left antecubital fossa. Cerebral and pulmonary edema, acute congestion of the inner organs, and mild atherosclerosis of the great arteries and the coronary arteries

were observed. The toxicological analysis of femoral venous blood revealed 3.9 μg/mL of propofol and 0.2 μg/mL of diazepam. Death was attributed to a self-administered therapeutic dose of propofol and diazepam without respiratory assistance. The manner of death was classified as suicide.

Case 3

A 36-year-old male ICU nurse was found dead in his apartment. An infusion catheter which was attached with an infusion bottle (500 mL) containing a little milky-colored fluid was inserted in the left antecubital fossa. **On the infusion bottle, sentence was written which implied his suicide.** External examination showed a fresh puncture mark in the left antecubital fossa. Most of the internal organs had undergone moderate putrefactive change and there were no obvious preexisting pathological findings. Toxicological analysis of femoral venous blood revealed 13.0 μg/mL of propofol, 3.1 μg/mL of midazolam, and 0.3 μg/mL of diazepam. Death was attributed to a self-administered overdose of propofol and midazolam along with a therapeutic dose of diazepam. The manner of death was determined to be suicide.

Case 4

A 41-year-old female **anesthesiologist** was found dead in a night-duty room in the hospital. Inserted into the vein of the right forearm was an infusion catheter, attached to an infusion bottle (50 mL) of 2% propofol containing a little milky-colored fluid. A suicide note was found in the room nearby. Multiple fresh puncture marks were observed on the anterior surface of both forearms. The autopsy revealed brain edema, pulmonary edema, acute congestion of the inner organs, and a filled urinary bladder. Toxicological analysis of femoral venous blood revealed 2.4 μg/mL of propofol and 2.3 μg/mL of amiodarone. Death was attributed to a self-administered therapeutic dose of propofol and amiodarone without respiratory assistance. The manner of death was determined to be suicide.

Case 5

A 54-year-old female anesthesiologist was found dead in her apartment. An empty bottle (50 mL) of 2% propofol and two used injection syringes were found next to the body. The woman had a long-term history of a depressive disorder and previous suicide attempts. External examination revealed multiple fresh puncture marks on the back of the right hand, anterior surface of the left wrist, and on the back of both feet. The only pathological findings were pulmonary edema and acute congestion of the inner organs. Toxicological analysis of femoral venous blood revealed 2.7 μg/mL of propofol and 0.05 μg/mL of mirtazapine. The cause of death was rapid self-administration of a therapeutic dose of propofol without respiratory assistance. The manner of death was suicide.

Case 6

A 46-year-old male **ICU** nurse was found dead in his apartment. Two partly empty and five unopened infusion bottles (50 mL) of 2% propofol and two used injection syringes (10 mL and 20 mL) were found near the body. A suicide note was found. The autopsy elucidated multiple fresh puncture marks on the back of both hands, pulmonary edema, acute congestion of the internal organs and a filled urinary bladder. Cardiomegaly with mild to moderate atherosclerosis of the coronary arteries was observed. Toxicological analysis of femoral venous blood revealed 1.7 μg/mL of propofol, 0.06 μg/mL of morphine (0.02 μg/mL of free morphine), 0.01 μg/mL of piritramide, 0.01 μg/mL of codeine, 0.07 μg/mL of tramadol, and 0.03 μg/mL of diazepam. The cause of death was self-administration of various drugs (propofol, morphine and diazepam). The manner of death was determined as a suicide.

Case 7

A 43-year-old male **anesthesiologist** was found dead in his apartment. An empty ampule (5 mL) of remifentanil was found in his left hand. A partly empty ampule (5 mL) of metamizol and two used injection syringes (5 mL) were also found near the body. There was neither a suicide note nor any knowledge of previous suicide attempts. External examination revealed multiple fresh and older puncture marks on both antecubital fossae, forearms and on the backs of both feet. The autopsy showed brain edema, pulmonary edema, and acute congestion of the internal organs. Toxicological analysis of femoral venous blood revealed 27 μg/mL of 4-methylaminoantipyrine and 0.9 μg/mL of 4-aminoantipyrine both of which are metabolites of dipyrone. No other substances (including remifentanil) were detected in either blood or urine. Death was due to a self-administered overdose of dipyrone. Remifentanil may also contribute to death by facilitating respiratory depression. Since older puncture marks as well as more recent ones were observed, it was not determined whether the manner of death was a suicide or an accident (by unintentional overdose).

Case 8

A 26-year-old male nurse was found dead with early putrefaction changes in his apartment. **He had been working as a scrub nurse in the hospital operating theatre.** Two used injection syringes (5 mL) were found near the body. One of the syringes had “Fenta” on it in handwriting. A farewell letter indicating suicide was found. External examination detected two fresh puncture marks on the anterior surface of his left forearm. Most of the internal organs had undergone putrefactive changes. Toxicological analysis of muscle tissue was negative. Sufentanil was detected in the residual

fluid within the syringes. Death was attributed to self-administration of sufentanil without respiratory assistance. The manner of death was classified as suicide.

Case 9

A 54-year-old male **surgeon** was found dead in his own clinic. Empty ampules of alfentanil (10 mL) and piritramide (2 mL), and a used syringe were found next to the body. Unused ampules of diazepam and midazolam were also discovered near the body. Although a suicide note was not found, the man had financial problems with his clinic **and had previous suicide attempts**. External examination showed a fresh puncture mark in the left antecubital fossa. Autopsy revealed cerebral and pulmonary edema, acute congestion of the inner organs, and mild atherosclerosis of the great arteries. Toxicological analysis of femoral venous blood revealed 0.2 μg/mL of alfentanil, 0.04 μg/mL of piritramide and 0.02 μg/mL of midazolam. The cause of death was self-administration of an overdose of piritramide and therapeutic doses of alfentanil and midazolam without respiratory assistance. The manner of death was determined to be suicide.

Discussion

Deaths due to self-administration of intravenous anesthetic/narcotic agents are commonly seen in health care professionals [1, 25]. **As observed in our cases (except case no. 1)** and compared with other branches of these professions, there is a higher incidence of such deaths among **anesthesiologists, surgeons, critical care physicians, and nurses of ICU or operating theatres** with easy access to these substances [1, 17]. Unintended environmental exposure to the substances in the workplace is also a risk factor for suicide attempts as well as drug addiction [26]. **In all 8 cases the anesthetic/narcotic agents used were clearly obtained from their workplaces.**

At the scene of death, catheters or syringes were found still inserted into or near the body. In accordance with other findings (eg, police investigations, suicide notes, anatomically reachable sites of injection) all our cases were suicides or accidents as disposal of the materials before loss of consciousness after administration would be impossible. In contrast, such materials are usually discovered more distant from the body in homicide cases [21, 27].

Intravenous anesthetic/narcotic agents detected in our cases were classified into 3 categories: propofol, opioids and benzodiazepines. They were administered solely in 4 cases (nos. 4, 5, 7 and 8) or in combination with other potentially fatal drugs in 5 cases (nos. 1, 2, 3, 6 and 9).

Propofol was detected in 6 cases (nos. 1-6) and was the most common agent. It is widely used to induce and maintain general anesthesia and to provide procedural sedation [28]. Psychological dependency because of the euphoria and sexual fantasies following injection in addition to rapid onset and ultra-short duration of the action can lead to its abuse [29, 30]. Subsequently, more deaths related to self-administration of it accidentally than those due to suicide attempts have been reported [12-21]. In contrast, all 6 of our cases were suicides. Except for case no. 4, propofol was detected in combination with opioids and/or benzodiazepines. Since propofol causes severe pain during intravenous administration [28], the deceased possibly used other agents to reduce the pain. In addition, there are two formulations of propofol available: 1% and 2%. In most of our cases, the 2% formulation was used, possibly because it may induce loss of consciousness more quickly, thus also decreasing any pain from the injection [31].

In 4 cases (nos. 2, 4, 5 and 6) with propofol, blood concentrations (Table 1) were within the therapeutic range (1.3-6.8 μg/mL, [1]). Interestingly, the concentration in previous reports ranged from 0.026 to 5.3 μg/mL, which was below or within the therapeutic ranges. Despite an injection of propofol overdose, its blood concentration cannot exceed the range because of the rapid decline from the blood through redistribution and metabolism [28]. In the relevant literature authors also suggest that overly rapid or rapid continuous injection of even a normal dose of it without respiratory assistance can cause prolonged apnea, extreme hypoxia and hypotension resulting in death [12-21]. Propofol was likely administered continuously through a catheter in case nos. 2 and 4, and injected overly rapidly via a syringe in case nos. 5 and 6. Accordingly, death might occur following an injection of propofol only in these cases. Moreover, severe and potentially fatal complications associated with propofol administration (eg, sepsis, acute pancreatitis, and propofol-infusion syndrome) are known clinically [28]. Although no complications were observed here, gross findings may be subtle. These potential complications may still represent the underlying pathophysiological mechanism of death when therapeutic levels of propofol are detected. In contrast, in 2 cases (nos. 1 and 3) blood propofol concentrations greatly exceeded the therapeutic range (Table 1) and undoubtedly led to fatal poisoning. In a suicide case by self-administered 1,600 mg of propofol via infusion, blood propofol concentration was merely 2.5 μg/mL [13]. It would thus seem that the deceased in 2 cases **could** have mixed a much larger dose of several thousand or more milligrams of propofol in the bottle and administered it rapidly.

Opioids such as fentanyl analogues (alfentanil, remifentanil and sufentanil), morphine, codeine, piritramide and tramadol were used in 5 cases (nos. 1, 6, 7, 8 and 9).

Fentanyl and its analogues are potent short-acting narcotics [5]. Fatalities due to intravenous self-administration of fentanyl among health care professionals have been well documented [2-8]. In contrast, only a few deaths have been reported related to recent fentanyl analogues such as alfentanil, remifentanil and sufentanil [10, 11].

In case nos. 1 and 9, alfentanil was detected in the blood at concentrations of 0.1 μg/mL and 0.2 μg/mL respectively, both within the therapeutic range (0.05-0.4 μg/mL, [32]). Alfentanil could contribute to death by enhancing the respiratory depressant effect of other agents in both cases. In case no. 7, remifentanil was not detected in the blood despite an empty ampule of it found at the scene. Pharmacokinetically, remifentanil is more rapidly eliminated from the blood via metabolization by elastases that are widespread throughout the blood in comparison with other analogues that depend upon hepatic biotransformation and renal excretion for elimination [33]. Only one fatal case associated with self-administered remifentanil has been reported, and remifentanil was also not detected in the blood in that case [11]. In the case here, a toxic level of dipyrone metabolite [34], 27 μg/mL of 4-methylaminoantipyrine was detected in the blood, thus contributing to death. However, remifentanil possibly resulted in death with potent respiratory depressant effect. In case no. 8, sufentanil was not detected in muscle tissue most probably due to putrefaction although it was detected in the fluid of the syringes found at the scene. To date there is only one report [10] of suicidal self-administration of sufentanil, where its blood concentration was 1.1 ng/mL, this being within the therapeutic range (0.25-8.0 ng/mL, [35]). Since no other drugs were detected in case no. 8, the cause of death was given as self-administered sufentanil.

In case nos. 6 and 9, piritramide was detected in the blood within therapeutic range (0.003-0.03 μg/mL, [36]). Piritramide is indicated primarily for managing postoperative pain [36, 37]. It also displays an unusually low respiratory depressant effect because of slow equilibration between the plasma and the site of effect [36, 38].

Benzodiazepines (diazepam and midazolam) were detected in 4 cases (nos. 2, 3, 6 and 9) and all of them were used in combination with other agents. Intravenous diazepam (0.02-2.0 μg/mL, [5]) is indicated for treatment of status **epilepticus**, while midazolam (0.25-1.0 μg/mL, [9-11]) is applied to general anesthesia and preoperative or procedural sedation. The therapeutic concentration of diazepam in case no. 2 and both the supratherapeutic concentration of midazolam and therapeutic concentration of diazepam in case no. 3 contributed to death by facilitating the respiratory depressant effect of propofol. In case no. 6, the therapeutic concentration of diazepam contributed similarly. In case no. 9, however, death was not attributed to the subtherapeutic concentration of midazolam.

Alongside the anesthetic/narcotic agents, the antiarrhythmic amiodarone and the antidepressant mirtazapine were uniquely detected in case nos. 4 and 5 respectively. Both drugs were prescribed for known illnesses of the deceased. In case no. 4, the therapeutic blood concentration of amiodarone (2.3 μg/mL) might have contributed to death by facilitating hypotension. In case no. 5, the therapeutic blood concentration of mirtazapine (0.05 μg/mL) only stimulated the release of both norepinephrine and serotonin [39], but was not related to death. Furthermore, 1.2 mg/mL of ethanol was detected in the blood in case no. 1 only. The concentration was **non-lethal**, but a level sufficient to facilitate the effects of propofol and alfentanil.

When fatalities are suspected to be due to self-administered intravenous anesthetic/narcotic agents, a toxicological examination easily allows a clear-cut diagnosis. However, interpreting results may be occasionally difficult. Most of our cases demonstrated that blood concentrations of these agents were within the therapeutic range. Any possible underlying pathophysiological aspects of the process of dying could be interpreted according to the following considerations: i) agents such as propofol and opioids cause death dependent upon administration manner and speed, and condition (eg, without respiratory assistance, even at therapeutic levels); ii) agents such as benzodiazepines contribute to a fatal outcome by facilitating respiratory depressant effects of other agents combined with them. In addition, since prescription drugs as well as ethanol also influence the toxic effects of anesthetic/narcotic agents, it is essential to also analyze them quantitatively. Any **additive or synergistic** actions must be taken into consideration as well.

Key points

1. We are presenting a retrospective study of 9 cases of death related to self-administered intravenous anesthetic/narcotic agents.
2. All of the deceased were health care professionals and used intravenous anesthetic/narcotic agents obtained from the workplace.
3. Intravenous anesthetic/narcotic agents detected post mortem were classified into 3 categories: propofol, opioids and benzodiazepines. These agents were either administered solely or in combination. In most cases, femoral venous blood concentrations were within the therapeutic range.
4. Propofol and opioids (fentanil analogues and morphine) cause death dependent upon administration manner and speed, even at therapeutic levels.

5. Because prescription drugs and ethanol also influence the toxic effects of anesthetic/narcotic agents, it is essential to analyze them quantitatively as well.

Conflict of interest statement

None declared.

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