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REVIEW

The abuse potential of propofol

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Context. Propofol is a sedative-hypnotic prescription medication that is widely used in anesthesia, long-term sedation, and conscious sedation. It is short acting, effective, and, when used appropriately, safe. It is not a controlled substance by the U.S. Drug Enforcement Administration, suggesting that it has little potential for abuse. The objective of this review was to evaluate the evidence for the abuse potential of propofol. *Methods*. A systematic review of the medical literature was performed using the search terms: propofol, Diprivan, abuse, addiction, tolerance, misuse, and withdrawal. Six online literature citation databases and relevant bibliographies were searched for articles. *Results*. Seventy-two articles were identified for review and 45 were relevant to the topic. These articles described propofol's biochemical and pharmacokinetic mechanisms of action that lend themselves to its abuse, propofol's physical and psychological effects that make it alluring as a recreational drug, the current evidence supporting the possibility of tolerance to and withdrawal from propofol, the risk involved in recreational propofol use, and the evidence supporting current abuse of this medication. We found evidence to support propofol's abuse potential from a pharmacological and experiential standpoint with multiple reports describing tolerance, dependence, withdrawal phenomena, abuse, and death from recreational use. *Conclusions.* Propofol has alluring and addictive properties that lend itself to potential recreational abuse and dependence. We recommend that the U.S. Drug Enforcement Administration and other international agencies should consider regulating propofol as a controlled substance.

Keywords Propofol; Abuse; Tolerance; Dependence; Regulation

Introduction

Propofol (2,6-diisopropylphenol) has been used in anesthesiology since 1986[1] and is primarily used for conscious sedation and induction of anesthesia. It is currently an unrestricted medication in the United States. Although its clinical properties are well described, knowledge concerning its abuse potential has been slow to emerge. Until recently, it was not considered to have abuse potential. However, a growing body of literature is documenting propofol abuse in humans and abuse-like behavior in animal models. A survey of nurse anesthetists demonstrated changing trends in recreational drug use, citing propofol as the fourth most misused drug.[2] Although evidence indicates that the majority of propofol abusers are medical professionals,[3] propofol's potential for abuse among the general public has recently been highlighted by the media with the drug's potential role in Michael Jackson's untimely death.

Objectives

The objective of this review was to evaluate the abuse potential of propofol. We were also interested in characterizing the population that uses this medication recreationally, and in understanding propofol's allure as a recreational drug. Finally, we sought to make a recommendation regarding the need for U.S. Drug Enforcement Administration (DEA) restriction of propofol as a controlled substance.

Search strategy and selection criteria

We conducted a comprehensive search and review of the medical literature related to this topic, including the biochemistry and pharmacokinetics that relate to propofol's abuse potential, as well as case reports, investigations, and clinical trials pertaining to individual tolerance, addiction, or withdrawal. We searched multiple databases, including Cochrane, PubMed, CINAHL, GoogleScholar, MEDLINE, and PsycINFO using the terms propofol, Diprivan, abuse, addiction, tolerance, misuse, and withdrawal. In addition, we checked and cross-referenced bibliographies. The most recent search was carried out in February 2010. Articles written in English and French were included for review. Two independent reviewers assessed articles for potential relevance, methodological quality, and final inclusion. Articles included in this review were published in peer-reviewed journals and the lay press whose content addressed our research questions and included basic research, case reports, retrospective, cross-sectional and prospective trials, and review articles.

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Results

Seventy-two articles were deemed appropriate for review from the literature search. Forty-five articles were related to propofol abuse, withdrawal, tolerance, or related pharmacokinetics. Twenty-seven articles were excluded after review because the content was not related to the purpose of this review (e.g., adverse reactions, propofol infusion syndrome, pancreatitis, and dosing for sedation).

Pharmacological evidence for propofol's abuse potential

Pharmacokinetics play an important role in the abuse potential of medication. The pharmacokinetics of propofol, with rapid onset of generalized anesthesia at low doses, make its abuse potential low. However, evidence suggests that the biochemical effects and pharmacokinetics may actually facilitate the abuse potential of propofol at subanesthetic and anesthetic doses.[3–6]

Propofol is an alkylphenol formulated in an oil-in-water emulsion. It is a highly lipophilic intravenous (IV) anesthetic, with a rapid onset and short duration of action.[1] The pharmacokinetics of propofol are described by a three-compartment linear model with compartments representing the plasma, rapidly equilibrating tissues such as the brain, and slowly equilibrating tissues such as adipose.[7] Following an IV bolus dose, there is rapid equilibration between the plasma and highly perfused brain tissue, which accounts for the rapid onset of anesthesia. Rapid redistribution accounts for its short duration of action. Because of the short duration of the narcotic effect, propofol abuse is especially easy to hide[8] and its effects are no less enjoyable to the abuser. After distribution, propofol is almost totally metabolized in the liver through glucuronidation or *p*-hydroxylation with subsequent glucuronidation and excreted by the kidneys. Small amounts are eliminated without being metabolized.

Propofol is chemically distinct from other commonly used anesthetic agents and has no direct affinity to opiate, benzodiazepine, or *N*-methyl-D-aspartate (NMDA) receptors.[8] It has been shown, however, to have distinct effects on gamma-aminobutyric acid (GABA) receptors,[9] which are also potentiated by alcohol, barbiturates, and benzodiazepines. These substances have proven abuse potential in humans and laboratory animals.[9] Importantly, there is laboratory evidence that correlates between drugs that are abused by humans and drugs that are self-administered by laboratory animals.[9] Several animal studies have demonstrated that the IV reinforcing effects of propofol were comparable to those of the IV drugs with known abuse potential, such as barbiturates,[9–11] further supporting propofol's abuse potential in humans. Patel and colleagues[5] demonstrated that propofol increases the levels of the endogenous cannabinoid anandamide in mice, which binds to cannabinoid receptors in the hypothalamus and brain stem. This effect is thought to contribute to its sedative-hypnotic properties and potentially to its addictive potential. In addition, other studies[4,6] have shown propofol to effect the mesolimbic reward system, both in the ventral tegmental area and in the nucleus accumbens. This is an important finding, as other drugs with abuse potential such as opiates, amphetamines, and cocaine, are recognized to affect the mesolimbic reward system with the release of dopamine. Li and associates[6] demonstrated that nanomolar doses of propofol increase the discharge rate and excitability of dopamine neurons in the ventral tegmental area of the rat brain. The authors proposed that propofol increases extracellular dopamine concentrations, resulting in these effects. Pain and collegues[4] also demonstrated the increased levels of dopamine in the nucleus accumbens in rats given 60–100 mg/kg boluses of propofol. These findings provide pharmacological support for the potential propofol abuse in humans.

The allure of propofol

If propofol were a sedative agent without any psychotropic effects, then there would be little recreational incentive. However, there is evidence to suggest that propofol's effects are potentially pleasant and desirable. In two prospective, randomized, double-blind, placebo-controlled crossover trials, Zacny demonstrated that one-half of healthy volunteers found propofol's effects pleasurable and were significantly more likely to describe these effects as "high," "sedated," "coasting or spaced out," and "drunken," when compared to placebo.[12,13] There are multiple accounts of good dreams and sexual disinhibition or illusion, even amorous advances and physical embraces, by patients who are awakening from propofol anesthesia.[8,14–16] Personal accounts from case reports of propofol abusers describe their experience after injection of propofol as "pleasant," "euphoric," and "relaxing."[17–19] Unlike other recreational drugs, propofol has a very short duration of action with rapid recovery.[12] In one study, psychomotor impairment in high-dose propofol infusion (0.32 mg/kg loading followed by 2.0 mg/kg/h infusion) resolved within 15 min of discontinuation of the infusion.[12] This makes propofol abuse particularly easy to hide and, therefore, alluring.[8] Unlike most drugs used for sedation or anesthesia (e.g., barbiturates, opiates, benzodiazepines), propofol is not currently regulated under the U.S. Controlled Substances Act, making it more easily available to the potential abuser.[2]

Propofol tolerance

The question of tolerance is important when discussing abuse because tolerance is one of the diagnostic criteria for dependence in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) published by the American Psychiatric Association. In many cases, it is tolerance that creates the circumstances of abuse, such as spending more time and resources procuring and using the drug. As such, it is reasonable to suggest that drugs that exhibit tolerance are also those that can put people at risk for dependence, abuse,

and addiction, as opposed to strict misuse. The data regarding propofol tolerance are somewhat limited, with most of the literature coming from the intensive care unit (ICU) setting. In the ICU, propofol is frequently used for sedation during mechanical ventilation as an IV infusion and not through frequent boluses as in abuse. The literature review on this topic produced conflicting data.

In a cost–benefit analysis comparing short-, medium-, and long-term sedation with propofol versus midazolam in the ICU, investigators found a "tachyphylaxis" phenomenon in patients who received propofol for sedation for more than 144 h (n = 10).[20] They did not provide further details regarding how the level of sedation was assessed, the degree to which the dose was increased, or the number of patients who experienced this phenomenon. This was an observation and not one of the main endpoints of the study. The authors felt that because of the small sample size, no conclusions could be made.

In a study designed specifically to determine whether tolerance to propofol can be observed in ICU patients, Buckley[21] performed a prospective, within patient, noncomparative pilot study of 11 patients who were continuously sedated with propofol for between 5 and 10 days. Five of the 11 patients showed increasing clearance, whereas 3 of 11 patients required increasing doses of propofol with steady blood concentrations of the drug and steady sedation levels, possibly representing tolerance to the medication. However, unlike the other patients in the study, these three patients demonstrated statistically significant improvement in Acute Physiology and Chronic Health Evaluation II (APACHE II) scores over time, suggesting that the increasing propofol requirement could be correlated to improved clinical condition and not necessarily caused by patients' tolerance to the drug effect. The authors conclude that there were insufficient data to reach a firm conclusion regarding the possibility of pharmacodynamic tolerance.

One case report and two prospective studies examining tolerance had variable outcomes. The case report involved a 2-year-old boy undergoing sedation for 23 sequential doses of radiation for the treatment of rhabdomyosarcoma.[22] This report convincingly demonstrated the boy's tolerance to the drug. Toward the end of his treatments, the patient's induction dose had increased by 1600% to 18 mg/kg, which failed to induce anesthesia. His maintenance dose had increased 500% to 500 mcg/kg/min. The patient's weight did not change during this 6-week treatment course and ultimately his anesthesiologist changed his induction medication to ketamine. As a follow-up to this report, Setlock[23] conducted a prospective study over a 2-year period, including all 2-year-old children receiving propofol anesthesia for radiation therapy. There was no demonstrable tolerance in any of the six patients in the study. However, this was a very small cohort of patients and the study may not have been powered to detect a statistically significant difference. The authors concluded that there was no evidence to support tolerance to an induction dose of propofol. Cohen[24] performed a prospective, observational study in which 30 patients received boluses of propofol for sedation before electroconvulsive therapy. These patients underwent five consecutive treatments in a 1-month period. The investigators recorded the dose of propofol required for sedation, the length of convulsion, and the time to wakefulness. Thirteen of the 30 patients (43%) demonstrated tolerance to propofol. They required progressive increases in doses of the medication ($p = 0.03$) from the third treatment onward up to twice the original dose, as well as having shorter duration of convulsive activity ($p = 0.01$), and shorter time to full wakefulness starting at the fourth injection ($p = 0.03$). The authors concluded that there was a "tolerance-like" effect to the medication in almost half of their patients but were unable to demonstrate pharmacodynamic tolerance given the fact that blood levels of the medication were not measured and pharmacokinetic tolerance with increasing clearance could not be excluded. Regardless of the mechanism, this study demonstrated statistically significant increases in doses for the desired clinical effect. In addition, the study design mimicked abuse behavior with bolus injections and may be most applicable to the population in question.

Two adult patients treated for propofol abuse reported tolerance to the relaxing and euphoric effects of propofol. A 25-year-old man used 200 mg doses of IV propofol to treat headaches, which progressed to up to 15–20 injections on almost a daily basis. He reported tolerance for the relaxing and euphoric effects within the daily binges but only a "low level" of tolerance between binge episodes.[17] A 31-year-old healthcare provider began injecting 50 mg of propofol for feelings of depression. This occurred on a daily basis up to 100 times per day. He also reported a tolerance to the euphoric effect during repeated injections and low tolerance between binges.[18]

There have been several animal studies that investigated propofol tolerance. One study examined time to wakefulness in three groups of 42 total rats receiving two constant bolus injections of propofol 10 mg/kg at times 0 and either 24, 48, or 72 h later.[25] The authors found significantly decreased sleeping time in the rats that received the second dose at 24–48 h but not 72 h. The blood concentrations of propofol did not differ between groups on awakening, suggesting that tolerance and not increased metabolism were responsible for the decrease in sedation time. In another study involving six mechanically ventilated rabbits sedated with a propofol infusion, all rabbits developed tolerance to the sedative effects of the medication within 1 h of beginning the infusion.[26] There were two phases of tolerance. In the first phase, the infusion rate increased while propofol concentration stayed the same indicating increased clearance or pharmacokinetic tolerance. In the second phase, propofol concentrations increased together with the infusion rate, indicating pharmacodynamic tolerance. These findings suggest a potential for tolerance to propofol, however, given the study design with propofol infusion rather than boluses they may be more generalizable to the ICU setting.

In summary, several studies suggest that there may be the potential for tolerance to propofol, either by increased clearance of the drug or by changes in the body's sensitivity to the drug's effects. It is difficult to generalize the studies whose subjects are receiving a continuous infusion of the medication to the potential abuse population. The limited data in which boluses were given to study subjects and an individual who was abusing propofol suggest that tolerance to propofol may be seen in some individuals.

Evidence supporting the possibility of propofol withdrawal

Like tolerance, the possibility of withdrawal is important in determining propofol's abuse potential. The literature regarding withdrawal from propofol consisted primarily of case reports from ICUs, which have the most experience with prolonged propofol infusions. This literature suggests that withdrawal from propofol is a phenomenon that is primarily seen in long-term sedation.[20,27–30]

Propofol, like benzodiazepines, acts through gamma-aminobutyric acid A receptors to produce anesthetic and sedative effects. It is reasonable to postulate that this common biochemical pathway could result in a common withdrawal syndrome.[19,31] Two case reports describe benzodiazepine-like withdrawal syndromes in patients thought to be withdrawing from propofol. The first involved a 41-year-old man sedated for 5 days postoperatively after repair of an extensive aortic dissection and described a withdrawal syndrome similar to that expected from benzodiazepine withdrawal, including tremulousness and a grand mal seizure. The seizure responded well to diazepam and the remainder of his symptoms resolved after restarting both the propofol and the opiate infusions.[30] In response to this report, Grant[32] pointed out that convulsions may complicate cardiopulmonary bypass with deep hypothermia and circulatory arrest and may also complicate aortic dissections that involve the ascending aorta. Furthermore, they called attention to propofol's documented anticonvulsant properties and suggest that propofol may have suppressed underlying epileptic activity until it was withdrawn. In critically ill patients, it is difficult to know whether tachycardia, agitation, or seizures represent withdrawal symptoms or changes in the clinical course that may have occurred regardless of propofol discontinuation. Such examples of withdrawal syndromes after long-term propofol infusion may not be generalizable to the scenario of propofol abuse, which typically occurs through IV bolus administration rather than constant infusion.

The second case of benzodiazepine-like withdrawal symptoms involved a 30-year-old physician who was admitted to the ICU following a motor vehicle collision in which he sustained a femur fracture.[19] At the time of admission, his caretakers were unaware that he had been using propofol on an almost daily basis for 1 year. He became tachycardic, diaphoretic, anxious, and restless. The patient then revealed his propofol use history and his symptoms were thought to be related to withdrawal from propofol. He was treated with gabapentin and his symptoms eventually improved. Later, the patient noted that he had tried to stop using propofol for about 2 weeks, during which time he experienced such severe cravings for the drug that he was very restless, had difficulty concentrating and sleeping, and ultimately went back to using propofol.

Conversely, several personal accounts from propofol users report few adverse or withdrawal symptoms. A 31-year-old general practitioner who was treated for propofol abuse of up to 5,000 mg/day reported "an almost complete lack of withdrawal signs" but admitted to intense craving upon cessation.[18] An anesthesiologist who was treated for propofol dependence stated that early in his abuse of the medication he experienced only sleep and a little "fuzziness," with "no other side effects."[33] However, as his use continued he began injecting more often, up to 10–15 times per day, and reported that "by this time he was no longer using propofol because of stress but because he had an overwhelming compulsion and craving to use the drug again." Although these are personal experiences and anecdotal data, they suggest that individual experiences with propofol vary from the enjoyment of its effects to its metabolism, tolerance, and even withdrawal. At this time, there is insufficient data to determine whether a propofol withdrawal syndrome exists. Animal models may be of benefit in future clinical research on this topic.

Propofol abuse

Multiple articles and case reports document the problem of propofol abuse. Although the majority of cases involved healthcare providers,[18,34,35] especially anesthesiologists and nurse anesthetists,[2,36–38] propofol use among lay people is also documented.[15,17]

To date, there are at least 45 documented cases of human propofol abuse or dependency that have been published in peer-reviewed literature between the years of 1992 and 2009, including Michael Jackson's recent death.[3,7,15,17,18,33,34,37–41] Of these 45 cases, 40 (89%) were medical professionals and 18 (40%) resulted in fatality. Of the deaths related to propofol, 15 (83%) were medical professionals. In a survey of U.S. anesthesia training programs, 38% (6/16) of residents in training who were reported to abuse the drug were found dead as the first sign of abuse.[37] Despite familiarity with propofol's appropriate use, dosing, and risks, medical professionals appear at high risk for death as a result of propofol abuse. It is likely that many more cases of recreational use have gone unreported. Current evidence supports an increasing incidence of recreational propofol use among health professionals over recent years.[36,37] Wischmeyer surveyed all 126 academic anesthesiology training programs in the United States to evaluate the prevalence of propofol abuse.[37] One or more incidents of propofol abuse or diversion were reported by 23 (18%) of these departments over the 10-year period from 1995 to 2005. This was a fivefold increase compared to previous studies indicating an important and largely unrecognized problem.

Potential risks with recreational use of propofol

Although propofol is widely used in the healthcare setting for general anesthesia and conscious sedation, without proper monitoring it can be very dangerous. One case report suggested that propofol can result in life-threatening apnea with just a single injection.[8] Factors affecting the drug's effects, such as drug redistribution, half-life, and clearance, can vary widely from person to person.[2] The same dose can have a range of effects, from light sedation to apnea. According to some estimates, apnea can persist for up to 3 min with risk of irreversible and potentially lethal hypoxemia.[1] The majority of deaths related to propofol abuse are thought to be due to respiratory depression.[3] However, Riezzo[40] reported a death related to cardiac toxicity in a 26-year-old anesthesiology resident who was found unconscious after injecting propofol. During his course in the ICU, he developed Brugada-like ECG changes preceding ventricular fibrillation and cardiac arrest. On autopsy, he had massive pulmonary and cerebral edema as well as myocardial contraction band necrosis with increased tumor necrosis factor (TNF)-α and cardiac apoptosis. The authors hypothesized that chronic propofol abuse may have contributed to his cardiac necrosis and arrest. A similar syndrome of Brugada-like ECG changes before cardiac arrest was observed in trauma patients who died of propofol-related infusion syndrome,[42] further supporting the hypothesis that propofol may be myotoxic.

Roussin[3] reported autopsy findings of hemorrhagic pancreatitis in a different fatal intoxication with propofol. Pancreatitis is a rare but known side effect of propofol;[43] and if hemorrhagic, pancreatitis could cause significant morbidity or mortality for the abuser.

In addition to the potential physical harm related to propofol abuse, there is evidence to support propofol's addictive potential. Case reports describe significant psychological dependence as evidenced by frequent relapse, strong cravings, loss of control, and continued use despite negative consequences.[3,19,33] As is characteristic of other drugs of abuse, propofol abuse has the potential to disrupt jobs, families, and lives. Additionally, on-the-job use by healthcare workers is potentially harmful to patients.

Regulation of propofol

The prevalence of propofol abuse by the general public is unknown but likely to be very low compared to other sedative drugs, with only a few cases reported over the last 20 years. Propofol can be relatively easy for healthcare workers to obtain because of its frequent use in the clinical setting and lack of restriction by the U.S. DEA. There is evidence that academic anesthesiology departments in the United States without control measures for dispensing propofol are significantly more likely to have deaths related to propofol misuse or abuse.[37] Given the apparent increasing incidence of propofol abuse by healthcare providers[2,37] and the potential for disruption of work, morbidity, and mortality from this abuse, stricter propofol regulation should be considered. Fospropofol, a water-soluble prodrug of propofol, was classified as a controlled substance (Schedule IV) by the DEA on November 5, 2009, stating that its abuse potential was comparable to its metabolite, propofol.[44] It is only logical that this restriction be extended to propofol itself.

Some authors are concerned that propofol regulation would impede ready access to a medication that is commonly used for urgent and emergent procedures.[37,45] The importance of having propofol readily availabile in these emergent situations is tempered by its abuse and misuse potential. An appropriate system of regulation can balance these risks and benefits. Recognizing this dilemma, some U.S. hospitals are already addressing the problem by regulating propofol availability. Wischmeyer[37] found that 29% of academic anesthesia departments had some regulation of access to propofol, and providers at these departments were less likely to abuse propofol as a result. In addition, an anesthesia department in Iowa specifically described its experience with a case of propofol misuse among one if its staff, after which they successfully instituted limitations on propofol availability.[41] This suggests that safe and effective propofol regulation is both possible and beneficial. Hospitals can implement secure systems for propofol storage that allows for ready availability in emergent situations.

Conclusion

There is pharmacological and clinical evidence that supports the abuse potential of propofol. Because of its short duration of action and lack of obvious withdrawal symptoms, its abuse may not be readily apparent to coworkers or friends. Propofol is a deceptively dangerous drug with the potential for tolerance, psychological dependence, and mortality when used for its pleasurable characteristics. It should be considered for controlled substance regulation by the U.S. DEA and other international agencies.

Declaration of interest

The authors have no conflict of interests. There was no outside funding for this review.

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