American Society of Anesthesiologists

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December 21, 2010

Christine A. Sannerud, Ph.D.
Chief, Drug and Chemical Evaluation Section
Drug Enforcement Administration
8701 Morrissette Drive
Springfield, VA 22152

RE: Docket No. DEA–338, Schedules of Controlled Substances: Placement of Propofol Into Schedule IV

Dear Dr. Sannerud:

On behalf of the American Society of Anesthesiologists (ASA), thank you for the opportunity to provide comments to the Drug Enforcement Administration (DEA) regarding the placement of the drug propofol into schedule IV of the Federal Controlled Substances Act. For the reasons outlined below, **ASA strongly supports DEA's proposal to place propofol into schedule IV of the Controlled Substances Act and believes that schedule IV is the proper schedule for the drug.**

While ASA is extremely supportive of DEA's proposal**,** we also remind the Agency that the U.S. health care system and the anesthesia community in particular, are currently recovering from a nationwide shortage of propofol and other related induction agents. We therefore urge the Agency to carefully consider the impact scheduling will have on the supply and distribution of propofol in the near-term in order to avoid unnecessary shortages that could hamper our ability to provide safe patient care. Specifically, we ask that DEA consult with FDA, manufacturers, wholesalers, distributors and hospitals before issuing a final rule scheduling propofol to ensure they are prepared to meet the more stringent requirements that come with the manufacturing, distribution and storage of a scheduled drug. Delaying or staggering the full implementation of scheduling may be necessary to ensure that supplies of propofol, the most commonly used anesthetic in the country, will remain readily available to patients undergoing surgery or other procedures requiring sedation. ASA believes that the scheduling of propofol will ultimately reduce harm to individuals who seek to abuse, misuse or divert propofol. However, as we have seen recently, many more patients will be harmed or put at greater risk if propofol is not available due to problems that could be averted by a more measured approach to scheduling of this important drug.

By way of background, ASA was founded in 1905 and currently represents more than 45,000 physician members. ASA is a national educational, research and scientific association of physicians that has, as a primary mission, the elevation and maintenance of the standards for the medical practice of anesthesiology with the goal of improved patient care. A necessary component of providing safe anesthetic care is the health and welfare of the physicians and other health professionals who provide that care. This responsibility to the health of our colleagues and the safety of our patients is the motivating factor for our comments today.

ASA was actively involved in 2008 and 2009 in providing comment and testimony during the new application and scheduling processes for the drug fospropofol. Propofol is the pharmacologically active metabolite of fospropofol and the two products share most pharmacological properties. Accordingly, ASA writes in support of FDA's recommendation to place propofol into schedule IV along with the newly classified fospropofol.

Pharmacological Effect

Propofol is an intravenous, sedative-hypnotic agent commonly used for sedation and general anesthesia in patients undergoing diagnostic or therapeutic procedures, and for sedation of mechanically ventilated patients in intensive care units.

The primary anesthetic action of propofol is thought to be produced by positive modulation of the inhibitory function of the neurotransmitter gama-aminobutyric acid (GABA) through GABA-A receptors. Other potential sites of action of propofol include strychnine sensitive glycine receptors, glutamate sensitive N-methyl-D-asparate receptors, and dopamine sensitive receptors in the mesocorticolimbic circuit of reward. Many of the potentially addictive drugs that are found in schedule IV act through mechanisms similar to propofol.

Propofol is marketed as an intravenous general anesthetic. As such, it shares with most other general anesthetic drugs the following primary pharmacologic actions: rapid loss of consciousness, respiratory depression with the potential for hypercarbia and hypoxemia, and cardiovascular depression causing hypotension and arrhythmia. There is a wide range of differences in the concentration-response curve for each of these effects among different individuals. The potency of the primary pharmacologic effects and the potential for variability in response make propofol a particularly dangerous drug in the uncontrolled environment of self-administration or recreational abuse.

Potential for Abuse

At nanomolar concentrations, propofol increases the spontaneous discharge rate of dopamine neurons in the ventral tegmental area of the midbrain (VTA). At these concentrations glutamatergic transmission to the VTA is also enhanced. [1] At subanesthetic and anesthetic doses, propofol increases extracellular dopamine concentration in the nucleus accumbens (NA). The VTA and the NA are main components of the dopamine reward system. This cellular action can manifest clinically as euphoria during recovery from anesthesia. [2]

A number of in vivo studies in laboratory animals and human volunteers have demonstrated the abuse potential of propofol.[3,4] Propofol elicits many of the rewarding and reinforcing responses seen in other schedule IV drugs, such as feelings of euphoria, light headedness, sedation and the production of pleasurable dreams. [4-6] Euphoria, for example, is frequently reported after propofol exposure. In one study of human volunteers, propofol was selected as the drug of choice by study subjects specifically because of its pleasant side effects. [4]

Clinical doses of propofol produce subjective responses commonly reported with other drugs that are frequently abused. These include: a rapid onset, a sense of euphoria, light headedness, and sedation.[7] Hallucinations and disinhibiton are frequently reported. Many patients and experimental subjects report pleasant dreams which sometimes contain sexual content.

History and Current Pattern of Abuse

Case reports of the recreational self-administration of propofol first appeared in 1991.[8] A number of individual reports have followed. [9-14] In many of these cases, propofol was the final drug used in a sequence that began with opiates or benzodiazepines and ended (in some cases in death) with propofol.

Epidemiologic studies have shown that propofol abuse is most common among health care professionals. Even in this population it remains relatively rare as a drug of abuse as compared to other drugs, such as opioids and benzodiazepines. However, the occurrence of propofol abuse is increasing in frequency. One recent survey observed that 18% of academic anesthesiology departments reported one or more incidents of propofol abuse.[15] The authors commented that their study probably underestimated the numbers because of the lack of routine testing for propofol and the difficulties associated with detecting propofol abuse. Despite the potential underreporting, this observed incidence rate of 10 per 10,000 anesthesia providers per decade represents a five-fold increase from a survey conducted 10 years previously.[16] Propofol abuse has also been reported among other physicians,[17] nurses, [8] nurse anesthetists,[9,13] ancillary health professionals,[18] and even in the lay population.[11] Of the 25 cases in the 2007 study of academic centers, 16 involved residents, 5 were attending anesthesiologists, 3 involved nurse anesthetists and one was an OR technician.[15]

Scope, Duration, and Significance of Abuse

Propofol abuse has been associated with a heightened risk of death.[19] In one review, death occurred in four of the nine individual case reports of propofol abuse.[7] And in a study that examined propofol abuse in American anesthesia residency programs, there were 7 deaths as a result of propofol overdose among the 25 reported individuals abusing propofol.[15] The authors of this study commented on the fact that deaths occurred only in programs in which there was no pharmacy accounting for the drug.

Death from self-administered propofol has usually been attributed to respiratory arrest. [7] Respiratory arrest is an easily treated side effect when the drug is properly administered by experienced clinicians, but rapidly fatal in the uncontrolled and unsupervised environment of self-administration.

Public Health Risks

Propofol abuse is a limited risk to the public. Because relatively large volumes must be injected in order to achieve an effect, it is difficult for the casual abuser, outside the hospital, to obtain the necessary equipment and technical knowledge to use this drug. However, there is greater concern for medical professionals who have ready access to intravenous supplies and skill in venous cannulation.

Psychic or Physiological Dependence Liability

Dependence from propofol is mostly psychological, characterized by craving, loss of control over the amount and frequency of drug required to achieve the desired effect, and continued use despite adverse consequences. No signs of physical dependence have been described, although withdrawal phenomena have been reported after prolonged use. [20]

Recommendation

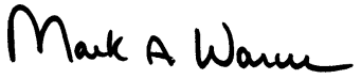
Propofol is now the most common drug used in this country for providing deep sedation and for induction of general anesthesia. It is widely used in virtually every hospital and ambulatory surgery center, as well as many physician and dentist offices. It has proven to be especially valuable in acute emergency situations where rapid onset and recovery are important. Because of its importance in acute care settings and emergency situations we feel that it should remain readily available for appropriate use by responsible clinicians.

However, like all powerful drugs with addiction liability, it should be safely stored and maintained in a restricted and secure environment with access limited only to qualified clinicians. We feel that the classification of propofol as a schedule IV drug, similar to many other sedative and anesthetic drugs (including the recently scheduled drug fospropofol), strikes the proper balance of maintaining appropriate availability for optimal patient care while restricting access and discouraging diversion.

In conclusion, for the reasons stated above, ASA respectfully requests that the DEA place the drug propofol into schedule IV of the Federal Controlled Substances Act. In addition, for the reasons mentioned in the introduction, ASA requests that the DEA proceed with caution when issuing any final rule to schedule propofol to avoid any disruption in the already fragile supply chain for propfol.

Thank you for the opportunity to offer our comments and we look forward to working with you on this important matter. Should you have questions on this issue please do not hesitate to contact Chip Amoe, JD, MPA, Assistant Director – Federal Affairs, in our Washington office at (202) 289-2222 or c.amoe@asawash.org.

Sincerely,



Mark A. Warner, M.D.
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