American Society of Anesthesiologists

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

RE: Docket No. DEA–327, Schedules of Controlled Substances: Placement of Fospropofol Into Schedule IV

Dear Dr. Sannerud:

The American Society of Anesthesiologists (ASA) commends you and the Drug Enforcement Administration (DEA) for the proposal to place fospropofol disodium injection (Lusedra®) (hereinafter "fospropofol") into schedule IV of the Controlled Substances Act (CSA). ASA fully supports this action and agrees with the findings of the scientific and medical evaluation that formed the basis for the DEA's decision.

By way of background, ASA was founded in 1905 and currently represents more than 43,000 physician and other professional members. ASA is a national educational, research and scientific association of physicians devoted to 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 active in providing testimony during the FDA's Anesthetic and Life Support Drugs Advisory Committee meeting on May 7, 2008, to review the new drug application for fospropofol. At that time, our testimony was directed towards the necessity to include the so-called "anesthesia training warning" in the labeling. Our main point was that fospropofol acts as a "prodrug" for the active metabolite propofol, which is a powerful anesthetic drug. The following comments are a continuation of that argument and are offered to support the DEA's proposal to classify fospropofol as a schedule IV controlled substance employing evidence that fospropofol is a potentially addictive and dangerous drug based upon the known experience with propofol.

Pharmacological Effect

Fospropofol is an intravenous, sedative-hypnotic agent indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures. The primary action of fospropofol is to produce sedation or general anesthesia. Fospropofol is a water soluble prodrug that is rapidly hydrolyzed in patients, and derives its sedative and anesthetic actions by releasing propofol into the blood and tissue. The primary anesthetic action of the active metabolite propofol is thought to be produced by positive modulation of the inhibitory function of the neurotransmitter gama-aminobutyric acid (GABA) through GABA-A receptors.

Although fospropofol is not primarily marketed to produce general anesthesia, it shares many of the properties and side-effects of its primary metabolite propofol, which is a general anesthetic. These properties include respiratory and cardiovascular depression, and rapid loss of consciousness. Individual responses to propofol vary considerably because of wide differences in its concentration-response curve in different individuals. Because of this variability in its active product, the administration of fospropofol also can be unpredictable in that a small dose might produce a minimal effect but a repeated dose could suddenly produce a profound anesthetic effect. Obviously, this would be particularly dangerous in the uncontrolled environment of self-administration.

Potential for Abuse

Due to its very recent approval, the clinical experience with fospropofol is limited. However, propofol, its main active metabolite, is the most common drug used in this country for providing deep sedation and for induction of general anesthesia. Propofol is widely used in virtually every hospital and ambulatory surgery center, as well as many physician and dentist offices in this country. It has proven to be especially valuable in acute emergency situations where rapid onset and recovery are special virtues.

It was not until propofol became widely used in the clinical setting that its abuse potential became apparent. Because of the mechanisms of action shared by propofol and fospropofol, it is predictable that the potential for abuse will be similar among these two drugs. However, because of the differences in pharmacokinetics, the potential for adverse events in the drug abuser may actually be greater with fospropofol.

Fospropfol's major active metabolite, propofol, displays cellular actions that are exhibited by other Schedule IV drugs. 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. [2] This cellular action frequently manifests clinically as euphoria during recovery from anesthesia. [3]

A number of studies in laboratory animals and human volunteers have demonstrated the abuse potential of propofol.[4, 5] 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. [5-7] Euphoria, for example, is frequently reported after propofol exposure.[8] In one study of human volunteers, propofol was selected as the drug of choice by study subjects specifically because of its pleasant side effects. [5] These same responses can be expected to contribute to the abuse potential of the prodrug fospropofol.

Further, characteristics of fospropofol render it potentially more dangerous than propofol, if self-administered. There is a great deal of individual variability in the rate of delay from injection to peak effect. Also, there are large differences among individuals in their abilities to convert fospropofol to propofol, and to metabolize propofol to inactive products. Because of these characteristics, some individuals who self-administer fospropofol may be inclined to repeat dosing, which creates a stacking effect, thus enhancing the possibility of overdose.

This mechanism of self-administered overdose is less likely to occur with propofol where unconsciousness typically occurs within seconds of administering a therapeutic dose.

An additional concern is that, unlike many other sedatives, no antagonist or reversal agent exists for either fospropofol or propofol should too much be administered. This lack of a resuscitative antidote renders an inadvertent overdose with fospropofol even more dangerous, due to its delayed onset.

History and Current Pattern of Abuse

Since fospropofol has only recently received approval, its use has been limited. However, similarities to propofol provide a comparison. Case reports of the recreational self-administration of propofol first appeared in 1992.[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 when 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, [9] nurse anesthetists,[10,13] 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

One aspect of the abuse potential of fospropofol that is particularly alarming is the risk of death.[19] In one review of the literature, death occurred in four of nine individual case reports of propofol abuse.[20] And in a study that examined propofol abuse in academic anesthesia residency programs, 7 deaths resulted from 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. [20] Respiratory arrest is an easily treated side effect when the drug is properly administered by experienced clinicians, but can be rapidly fatal in the uncontrolled and unsupervised environment of self-administration.

Public Health Risks

Fospropofol and propofol are of limited risk to the public. Because relatively large volumes must be injected in order to achieve an effect, it will be difficult for the casual abuser, outside the hospital, to

easily access or use these drugs. However, there is greater concern for medical professionals who have ready access to intravenous supplies and skill in venous cannulation. The low risk of abuse by the public is a significant reason for ASA's support for the classification of the drug as a schedule IV.

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. [21]

Immediate Precursor of a Controlled Substance

As discussed previously, fospropofol is an immediate precursor of propofol. Although propofol is not currently a controlled substance, we have made the argument in this discussion that propofol shares characteristics with many schedule IV drugs.

Conclusion

For the reasons stated above, ASA once again applauds the DEA for its proposal to place the new drug fospropofol in schedule IV of the Controlled Substances Act. We anticipate that, similar to propofol, fospropofol will become a valuable addition to the therapeutic armamentarium for the administration of safe anesthesia. Therefore, classification as a schedule IV substance will allow fospropofol to remain readily available for use by responsible clinicians in urgent and emergent situations, similar to other schedule IV sedative and anesthetic drugs, including most benzodiazepines and barbiturates. However, it will be reasonably stored and maintained in a restricted and secure environment with access limited to qualified clinicians. We feel that the DEA's proposal strikes the proper balance of maintaining appropriate access for optimal patient care while restricting access to prevent abuse and diversion and protect health care providers.

Thank you for announcing a well-reasoned proposal and for the opportunity to offer our comments in support of your efforts. We look forward to working collaboratively with you on related matters in the future. 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,

Roger A. Moore M.D

Roger A. Moore, M.D.
President
American Society of Anesthesiologists

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