

*Advancing the
Art & Sciences
of Anesthesia
for 75 Years*



November 13, 2005

Division of Dockets Management (HFA – 305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: CITIZEN PETITION #2005P-0267
ATTN: Dr. Robert Rappaport, CDER

Dear Dr. Rappaport:

On behalf of the 33,000 members of the American Association of Nurse Anesthetists, and in the interest of the millions of patients for whom we provide care, we wish to underscore the importance of safe practice and patient safety in the administration of propofol in hopes that the agency will not alter its current “black box” warning. We are aware at least one organization has issued the agency a citizen petition (2005P-0267, 6/27/2005). We will demonstrate that the properties of propofol continue to demand that the current FDA warning concerning propofol be retained; as the FDA warning states, propofol “should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure.” We suggest that the argument of the citizen petition that the FDA ought to remove the warning from propofol on economic grounds is misplaced, and should be referred to the appropriate payors for healthcare services, including the Centers for Medicare & Medicaid Services (CMS).

As you may know, the AANA is the professional association for more than 33,000 Certified Registered Nurse Anesthetists (CRNAs) representing over 90 percent of the nurse anesthetists in the United States. Today, CRNAs administer more than 65 percent of the anesthetics given to patients each year in the United States. CRNAs provide anesthesia for a wide variety of surgical cases and are the sole anesthesia providers in almost 70 percent of rural

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2005P-0267

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hospitals, affording these medical facilities obstetrical, surgical, and trauma stabilization capabilities. CRNAs work in every setting in which anesthesia is delivered including hospital surgical suites and obstetrical delivery rooms, ambulatory surgical centers (ASCs), and the offices of dentists, podiatrists and plastic surgeons.

Properties and Administration of Propofol

The current FDA warning on propofol states:

For general anesthesia or monitored anesthesia care (MAC) sedation, DIPRIVAN® Injectable Emulsion should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. Patients should be continuously monitored, and facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.

For sedation of intubated, mechanically ventilated adult patients in the Intensive Care Unit (ICU), DIPRIVAN Injectable Emulsion should be administered only by persons skilled in the management of critically ill patients and trained in cardiovascular resuscitation and airway management.

In the elderly, debilitated or ASA III/IV patients, rapid (single or repeated) bolus administration should not be used during general anesthesia or MAC sedation in order to minimize undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction, and/or oxygen desaturation.

Several attributes of propofol justify this warning. Many of these attributes are published on the FDA Draft Final Printed Labeling for generic propofol (FDA, Application #075392, Gensia Sicor Pharmaceuticals, Approval Date 9/19/2000). Others relate to the literature, education and professional experience of CRNAs and anesthesiologists. Propofol is preferred for anesthesia care for many procedures, including certain gastrointestinal diagnostic procedures, because of the comparatively rapid dissipation of its sedative effects. Patients wake up from

propofol quickly, compared with other drugs used for sedation. However, unlike many other pharmaceuticals used for sedation or induction, there is no agent that reverses an overdose of propofol. Propofol overdose stops breathing, transitioning the sedation of the patient into a general anesthetic, and demanding the healthcare provider ventilate the patient and be trained in maintaining general anesthesia. Under many gastrointestinal procedures for which sedation is used, the patient lies prone and must be rolled over to ascertain and secure an adequate airway. The issue, therefore, is not whether a healthcare provider may or may not adequately administer propofol; it is whether a healthcare provider can adequately address the known complications of propofol administration to ensure patient safety.

Such experiential factors are buttressed by the FDA's own labeling, worth excerpting at some length here (FDA, Application #075392), and by the literature:

"Addition of a potent opioid (e.g. fentanyl) when used as a premedicant further decreases cardiac output and respiratory drive.

"During maintenance, propofol causes a decrease in ventilation usually associated with an increase in carbon dioxide tension which may be marked depending upon the rate of administration and other concurrent medications (e.g. opioids, sedatives, etc.).

"During monitored anesthesia care (MAC) sedation, attention must be given to the cardiorespiratory effects of propofol. Hypotension, oxyhemoglobin desaturation, apnea, airway obstruction, and/or oxygen desaturation can occur, especially following a rapid bolus of propofol. During initiation of MAC sedation, slow infusion or slow injection techniques are preferable over rapid bolus administration; and during maintenance of MAC sedation, a variable rate infusion is preferable over intermittent bolus administration in order to minimize undesirable cardiorespiratory effects....

"With increasing patient age, the dose of propofol needed to achieve a defined anesthetic end point (dose-requirement) decreases...."

The anesthesia literature since the FDA's 2000 approval of generic propofol further describes propofol's properties. Though propofol has well understood sedative properties, Drs. Frolich, Price, Robinson et al more recently found "subjects rated both pain intensity and unpleasantness higher when sedated with propofol.... This effect was unexpected and may be explained by a difference of subjective pain experience by a patient and the perceived level of analgesia by a healthcare provider in sedated patients. This finding calls further attention to the need for adequate analgesia in patients sedated with propofol." (Frolich M, Price D, et al. The effect of propofol on thermal pain perception. *Anesth Analg* 2005;100:481-6). An anesthesia professional interprets these findings by underscoring the consideration to administer opiates along with propofol to achieve sufficient analgesic and sedative effects, with the understanding that propofol's own labeling correlates such administration with apnea and hypotension demanding judgment and vigilance undistracted by the conduct of the surgical and/or diagnostic procedure.

In reviewing literature associated with emergency medicine and not procedural sedation studies that did not meet their particular criteria, Drs. Wilbur and Zed buttressed findings of the FDA approved labeling of propofol in stating that while propofol provided "markedly shorter induction and recovery times than midazolam...(a)pneic episodes (>30 seconds) occurred in 23% of propofol recipients, 28% of thiopental recipients, and 7% of etomidate and midazolam recipients.... Propofol is a cardiovascular depressant that causes dose-related blood pressure reductions.... In the 6 DCC (direct current cardioversion, parenthetical added) studies reviewed, 21 (23.3%) of 90 patients who received propofol experienced apnea episodes longer than 30 seconds." (Wilbur K, Zed P. Is propofol an optional agent for procedural sedation and rapid sequence intubation in the emergency department. *Can J Emerg Med* 2001;3:1 which references *Can J Anaesth* 1988;35:479-83, *Anaesthesia* 1990;45:872-5, *J Cardiothor Vasc Anesth* 1991;5:566-8, *Acta Anaesthesiol Scan* 1991;35:609-15, *Anesth Analg* 1993;77:690-4; *Crit Care Med* 1993;23:1509-13).

A critical care medical records study and literature review conducted by Kowalski and Rayfield further stated, "Decreases in blood pressure and heart rate are common after treatment

with propofol is started. Propofol may depress systemic vascular resistance and cardiac output, partly as a result of sympathetic inhibition.... (i)n both studies, recovery from deep sedation and weaning from mechanical ventilation were faster in the propofol group than in the midazolam group.” (Kowalski S, Rayfield C. A post hoc descriptive study of patients receiving propofol. Am Journ Crit Care 1999;8, which references Crit Care Med 1994;22:1415-1423) In addition, citing the 1994 text on use of propofol (DIPRIVAN®) in the intensive care unit, the authors state, “Although analgesic requirements may be reduced during propofol therapy, in clinical trials, most patients required opiates for analgesia during maintenance of ICU sedation.”

The anesthesia literature underscores age and body mass index as factors in appropriate propofol dosage. (Niiyama Y, Omote K, et al. Effects of gender, age and body mass index on sedation level during infusion of propofol by target-controlled infusion. J Anesth 2002;96:A63) Tokumine, Sugahara and Tomori et al also found tissue necrosis caused by extravasated propofol. (Tokumine J, Sugahara K, et al. Tissue necrosis caused by extravasated propofol. J Anesth 2002;16:358-9)

Given the literature and the data, it is clear that training in the administration of general anesthesia (including the administration of narcotics) and in managing its known properties, physiological response based on patient and possible complications, are all required to assure patient safety with the administration of propofol. Based on the evidence, organizations representing the vast majority of anesthesia professionals have spoken decisively to this issue.

Professional Organizations Recommend Keeping Current FDA Warnings

In response to the proliferation of nurse-administered propofol sedation (NAPS), the AANA and the American Society of Anesthesiologists (ASA) published a Joint Statement Regarding Propofol Administration April 14, 2004

(http://www.aana.com/news/2004/news050504_joint.asp, and

<http://www.asahq.org/news/propofolstatement.htm>):

“Because sedation is a continuum, it is not always possible to predict how an individual patient will respond. Due to the potential for rapid, profound changes in sedative/anesthetic depth and the lack of antagonistic medications, agents such as propofol require special attention.

“Whenever propofol is used for sedation/anesthesia, it should be administered only by persons trained in the administration of general anesthesia, who are not simultaneously involved in these surgical or diagnostic procedures. This restriction is concordant with specific language in the propofol package insert, and failure to follow these recommendations could put patients at increased risk of significant injury or death.

“Similar concerns apply when other intravenous induction agents are used for sedation, such as thiopental, methohexital or etomidate.

*“*This statement is not intended to apply when propofol is given to intubated, ventilated patients in a critical care setting.”*

Subsequently, the Accreditation Association for Ambulatory Health Care endorsed the above statement “regarding the safe use of propofol and other intravenous drugs that do not have antagonist medications.” (AAAHC statement, 5/24/2005, http://www.aaahc.org/eweb/docs/prs_rel_propofol.pdf) The AAAHC reports having accredited more than 2,200 such organizations in the U.S.

An editorial in a healthcare industry journal has also expressed agreement with the AANA-ASA statement and the AAAHC statement. “Deleting this (FDA) warning (about propofol) would make it OK for endoscopists and gastroenterologists and RNs working under their supervision to push propofol. And that’s not OK. Not because the GI docs or nurses are incapable of administering the drug whose only reversal agent is time, but because they could never do so with the required level of safety.” (Parentheses added) (O’Connor D. Keep propofol in trained hands. Outpatient Surgery Magazine 2005:8;8)

It is important to underscore that the position of the AANA in particular is not founded on interprofessional “turf” but on longstanding professional judgment based in the literature and the data. In June 1996 and later in June 2003, the AANA published a document titled, “Considerations for Policy Guidelines for Registered Nurses Engaged in the Administration of Sedation and Analgesia.” (<http://www.aana.com/practice/conscious.asp>) The document cites standards from the AANA and the American Society of Anesthesiologists (ASA) in describing levels of analgesia and sedation, refers to the related standards published by the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO), and sets out guidelines for qualifications, management and monitoring of sedation and anesthesia services. The AANA’s recommended considerations further state, “The administration of sedation and analgesia requires constant monitoring of the patient and ability of the administrator to respond immediately to any adverse reaction or complication. Vigilance of the administrator and the ability to recognize and intervene in the event complications or undesired outcomes arise are essential requirements for individuals administering sedation and analgesia.” (AANA, June 2003) This statement compliments the validity of the FDA’s current labeling requirement for propofol in light of the literature and the data.

State boards of nursing charged with determining nursing scope of practice in their respective states have spoken to the issue of nurse-administered propofol sedation (NAPS). In 2003, 13 state boards of nursing reportedly expressly prohibited NAPS. By 2005, the number of boards of nursing expressly prohibiting NAPS reportedly had nearly doubled, to 23. (Schraag J. Legal aspects of conscious sedation and release. *EndoNurse* 2005;Aug-Sept)

Citizen Petition’s Reliance on Nonanesthesia Studies Weakens Its Case to Remove FDA Propofol Warning

The proponents of the June 27, 2005, citizen petition argue that their position is justified by 31 studies that the authors cite. The studies themselves tend to undermine the central thesis of the petition, that the FDA warning on propofol ought to be deleted so that nurses and nonanesthesia professionals might administer it without restriction. Of the 31 studies, one is

from what might be described as the anesthesia literature (Anaesth Intensive Care), and the other 30 are published from gastroenterology journals and a popular industry trade magazine.

Further, as stated in the June 27 citizen petition, 13 of the 31 studies were “uncontrolled,” which we understand to mean that they were not done prospectively or in an otherwise scientifically acceptable manner. Many of the studies seem to have involved large numbers of cases spread over considerable time. For example, the study by Tohda et al (Tohda G, Higashi S et al. Propofol sedation during endoscopic procedures: safety and effective administration by registered nurses, supervised by endoscopists [abstract]. *Gastrointest Endosc* 2005;61:AB123) involved 25,200 patients over seven years. A study by Baptista et al (Baptista A, Bonilla Y et al. Propofol sedation for gastrointestinal endoscopy administered by nursing staff under gastroenterologist supervision [abstract]. *Gastrointest Endosc* 2005;61:AB108) involved 7,000 procedures. These appear to have been retrospective, not prospective, studies. It seems possible, therefore, that some complications of propofol administration such as silent aspiration or pneumonias were not detected or considered. Studies identified as having been “randomized” were much smaller. Vargo et al (Vargo J, Eisen G, et al. Cardiopulmonary complications with non-anesthesiologist administered propofol vs. standard sedation: the CORI experience [abstract]. *Gastrointest Endosc* 2004;59:AB132) reported on 75 patients. Sipe et al (Sipe B, Rex D et al. Propofol versus midazolam / meperidine for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Gastrointest Endosc* 2002;55:815-825) involved 80 patients. Kongkam et al (Kongkam P, Pornphisarn B, et al. Non-anesthetist administered propofol for ERCP; efficacy, safety profile and side effect: a prospective randomized trial [abstract]. *Gastrointest Endosc* 2004;59:AB127) involved 75 patients. A study by Rex and colleagues (Rex D, Heuss L, Walker J. Nurse administered propofol sedation: safety record among individual nurses and physicians in 3 centers [abstract]. *Am Journ Gastroenterol* 2004;99:S300) involved 28,697 cases at three endoscopy centers, and another study by Rex et al (Rex D, Overley C et al. Safety of propofol administered by registered nurses with gastroenterologist supervision in 2000 endoscopic cases. *Am Journ Gastroenterol* 2002;97:1159-1163) involved 2,000 cases, but there is no indication that either study was prospective or randomized. It may have been that these were retrospective analyses based on past patient records. Of the 31 studies and articles cited by

the June 27 citizen petition, the only one clearly indicated to have been a more scientifically valid controlled randomized study was that by Ulmer et al (Ulmer B, Hansen J, et al. Propofol versus midazolam / fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. Clin Gastroenterol Hepatol 2003;1:425-432), involving 100 colonoscopy patients randomized to two groups.

With the smaller studies, the actual numbers of cases may have been too small for the results to be scientifically valid or reliable; the purported results may be statistically inaccurate or unreliable. If so, it would call into question the researchers' conclusions, especially to the extent that such conclusions are stretched to pertain to complications of anesthesia as the June 27 citizen petition suggests.

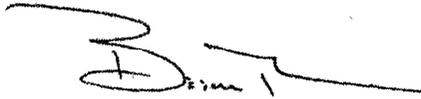
Conclusion

CRNAs are experienced and highly trained anesthesia professionals whose record of patient safety in the field of anesthesia – during which the Institute of Medicine found in 2000 that anesthesia is 50 times safer than 20 years previous (Kohn L, Corrigan J, Donaldson M, ed. To err is human. Institute of Medicine, National Academy Press, Washington DC, 2000) – enables us to comment knowledgeably on the safe administration of propofol. The labeling and literature of propofol administration underscore its uses, as well as its risks, which include hypotension, apnea, other compromises to the airway, and increased effects when administered in conjunction with opioids and/or for patients with certain underlying medical conditions (e.g., a history of congestive heart failure). The fact that many gastrointestinal procedures take place with the patient in a prone position places greater emphasis on the healthcare provider administering propofol to maintain vigilance over the patient's airway and vital signs, particularly the understanding that the anesthesia provider would be “competing for the airway” in procedures where a scope is placed through the patient's mouth. Anesthesia providers must also prepare for the known complication that propofol sedation may stop the patient's respiration and convert into a general anesthetic without a reversal agent available.

We recommend against removing the FDA-mandated warnings from propofol, on the grounds of patient safety. We suggest that the argument of the citizen petition that the FDA ought to remove the warning from propofol on economic grounds is misplaced, and should be referred to the appropriate payors for healthcare services, including the Centers for Medicare & Medicaid Services (CMS). It is likely the June 27 petitioners would agree with us that CMS' Part B schedules reimburse insufficiently for many gastrointestinal diagnostic procedures and under allocate the costs of the sedation component of such codes. The availability of relatively comfortable gastrointestinal diagnostic procedures correlates with the crucial public health goal of early diagnosis and treatment of colorectal cancers, and with improved quality of life for patients.

Thank you for your attention to this important patient safety issue. If you have further questions or comments, please contact Frank Purcell, AANA Senior Director Federal Government Affairs, 202-484-8400, fpurcell@aanadc.com.

Sincerely,



Brian Thorson CRNA MA
President, AANA

Frank J. Purcell
Senior Director, Federal Government Affairs



*Supporting Our Members --
Protecting Our Patients*

**American Association
of Nurse Anesthetists**
Federal Government Affairs Office
The Capitol Hill Office Building
412 First Street, SE, Suite 12
Washington, DC 20003

Phone: (202) 484-8400
Fax: (202) 484-8408
e-mail: fpurcell@aanadc.com
www.aana.com