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The Semantics of Ketamine

[Green SM, Krauss B. The semantics of ketamine. *Ann Emerg Med.* November 2000;36:480-482.]

"*The limits of my language are the limits of my world.*"[1]

Ketamine administration by emergency physicians to facilitate painful or emotionally disturbing pediatric procedures is now commonplace in emergency departments throughout the United States and Canada, and the historical barriers to ED use of this dissociative agent have for the most part been overcome. Several large series document a wide margin of safety for ED administration of ketamine,[2-8] and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has confirmed that ED ketamine administration is fully compliant with their standards when administered according to protocol.[9]

Despite widespread acceptance of ED ketamine administration for procedural sedation and analgesia (PSA), considerable confusion continues to surround its pharmacologic classification. Some anesthesiologists have labeled ketamine a "general anesthetic" because apnea and loss of airway reflexes have occurred when ketamine is coadministered with other agents. This has led to the unfortunate generalization that this is an inherent property of ketamine itself and therefore the drug is too dangerous to be used by nonanesthesiologists.[10-12] As a result of such arguments, some hospitals still craft their JCAHO-mandated sedation policies to exclude or excessively limit ED ketamine administration, thereby effectively depriving emergency physicians of a safe and effective tool to provide pain relief and anxiolysis for traumatized children.

To move past a semantic debate over what is and what is not "general anesthesia," we believe it is time for an evidence-based appraisal and classification of ketamine. In this editorial, we summarize the data demonstrating why ketamine is not a general anesthetic, and then cite and refute the opposing arguments. Finally, we propose a new classification for ketamine.

The first reason why ketamine is not a general anesthetic is that the effects of ketamine are inconsistent with standard definitions of general anesthesia put forth by the American Society of Anesthesiologists (ASA),[13] the American Academy of Pediatrics (AAP),[14] and the National Institutes of Health.[15] For all 3 definitions, the hallmark of general anesthesia is the inability to independently maintain spontaneous respirations and a patent airway. Throughout inhalational anesthesia, for example, markedly impaired respirations and airway reflexes are the norm. During general anesthesia, according to the ASA, spontaneous ventilation is "frequently inadequate" and airway intervention is "often required."[13] In contrast, ketamine consistently preserves upper airway muscular tone and protective airway reflexes, and spontaneous respirations are essentially always maintained.[3,8]

Second, the effects of ketamine are inconsistent with the classical stages and planes of general anesthesia. In his landmark 1937 work, Guedel[16] described 4 stages and 4 planes for the general anesthetic continuum.[16,17] Soon after the release of ketamine, however, it was quickly recognized that the unique dissociative effects of this drug did not conform to these expected stages/planes,[18,19] with one anesthesiologist commenting that ketamine "is not a general anesthetic in the accepted sense of the term."[19] In fact, rather than displaying the dose-response continuum observed with all other agents, ketamine is dichotomous—patients are either dissociated or they are not. This dissociation, once achieved, has no observable progressive depth or level, and administration of additional ketamine to an already dissociated patient does not enhance or deepen sedation as would be the case with opioids, sedative-hypnotics, or inhalational agents.[8] In the ASA and AAP sedation definitions/guidelines,[13,14,20] the more drug given, the more the patient progresses along the sedation continuum, with increasing probability of

impaired independent airway function and respiratory control. In contrast, the absolute amount of ketamine given has no impact on respiration and airway integrity within the range of clinically administered doses and using standard administration methods.

Finally, ketamine should not be considered a general anesthetic because it does not induce classic anesthetic-type electroencephalographic (EEG) suppression. General anesthetics exert their effects through global central nervous system (CNS) depression, as can be consistently evidenced through EEG waveform suppression during general anesthesia.[17] Ketamine works through an entirely different mechanism and exerts its effect by "disconnecting" the thalamoneocortical and limbic systems, effectively dissociating the CNS from outside stimuli (eg, pain, sight, sound).[8] Accordingly, ketamine does not significantly depress the CNS or EEG waveforms.[21,22] Bispectral EEG analysis techniques have been recently introduced that permit clinicians to effectively monitor the depth of sedation with inhalational agents, propofol, and midazolam.[23] Patients receiving ketamine, however, retain cortical function and fail to exhibit the expected depression of the bispectral index.[24]

The 3 common counterarguments that have been used to justify the labeling of ketamine as a general anesthetic are discussed below.

The first argument is that ketamine has always been, and should therefore remain, an "anesthesiologist's drug." Ketamine was introduced in 1970 to the anesthesia market, and the original research on this drug was performed by anesthesiologists.[8] Despite this, ketamine subsequently lost favor with anesthesiologists, and for many is now an extremely limited portion of their practice. Over the past 30 years, ketamine has become widely used by general practitioners throughout the developing world,[25-27] by veterinarians,[28] by emergency physicians,[2-8] and by various pediatric specialists.[2,8,29] To argue that ketamine must remain an anesthesiologist's drug is as unrealistic as maintaining that the ECG is solely a cardiologist's tool, or that interpreting radiographs is exclusively within the purview of radiologists. It is also important to note that the majority of drugs currently used by emergency physicians for PSA (eg, fentanyl, midazolam, barbiturates, and nitrous oxide) were all first studied by anesthesiologists and used in the operating room before becoming available in the outpatient setting.

The second argument is that ketamine is listed as a "general anesthetic" in the manufacturers' product labeling, as well as in many textbooks of anesthesiology and pharmacology. As noted earlier, such a classification does not accurately reflect the unique pharmacology of ketamine. Referring to ketamine as a general anesthetic in this setting reflects organizational convenience, rather than evidence that it is similar to anesthetic drugs.

The third argument, a logical corollary that follows from the first 2 arguments, is that ketamine is "too dangerous" for emergency physicians, for despite its broad and well-established margin of safety, rare airway-related adverse events can occur. Some will argue that only anesthesiologists can be relied on to promptly identify and manage such complications. However, emergency physicians by nature of their residency training are skilled in PSA, resuscitation, and advanced airway management, permitting them to effectively deal with potential sedation complications. Assuming that they are knowledgeable regarding the unique effects of ketamine (through training or experience) and are following a standard protocol,[9] emergency physicians can be readily considered qualified and competent with ketamine. Anesthesiologists may argue that permitting ketamine in the ED essentially guarantees that some sedation mishap will ultimately occur; however, there is no evidence that such complications might occur any more frequently than anesthesia mishaps in the operating room.[2-4]

To summarize these arguments, the unique ketamine dissociative state is fundamentally distinct both pharmacologically and clinically from that induced by general anesthetics, and cannot be compared with them on equal or even similar terms. Any attempt to lump ketamine in the same category as anesthetics is simply not evidence-based, and suggests an incomplete understanding of the distinct mechanism and effects of this drug.

So if ketamine is not a general anesthetic, how best should it be classified? When updating JCAHO-mandated sedation policies, individual hospitals have either labeled ketamine as "conscious sedation" or "deep sedation" (substitute "sedation/analgesia" for "conscious sedation" if your hospital policy is modeled after the ASA[20] rather than AAP[14] guidelines) or restricted ketamine use to anesthesiologists. Neither of these decisions is appropriate, as the ketamine dissociative state is inconsistent with standard definitions for both conscious sedation (which requires responsiveness to verbal/tactile stimuli[13,14,20]) and deep sedation (which requires responsiveness to painful stimuli[13] and "includes the inability to maintain a patent airway independently"[14]). The ASA and AAP sedation policies were not written with ketamine as a sole agent in mind.

Defining hospital monitoring standards based on traditional conscious sedation[14] (or sedation/analgesia[20])

guidelines makes the most sense if one feels compelled to stay within the realm of established terminology, as the appropriateness of this monitoring level for ketamine is both supported by extensive literature[2-8] and verified as compliant by the JCAHO.[9] Trying to "force" ketamine into a deep sedation mold is counterintuitive, because the added precautions stipulated[14,20] for this level of sedation are designed to detect adverse events commonplace during propofol or deep benzodiazepine/opioid sedation, but foreign to ketamine. Does it make sense to measure blood pressure every 5 minutes—as stipulated for deep sedation—when ketamine-associated hypotension has never been reported in a child who was not critically ill and in extremis? Does it make sense to require intravenous access to administer naloxone or flumazenil when these agents do not reverse ketamine?

We believe that trying to force ketamine into the existing ASA and AAP sedation guidelines is neither appropriate nor based on existing literature. Instead, we propose that the unique actions of this drug are best represented by a separate sedation category, "Dissociative Sedation," which we define as "A trancelike cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability." Monitoring guidelines and dosing recommendations for dissociative sedation can be supported by the existing ketamine literature. The authors are currently developing such a practice parameter. Focusing on evidence rather than semantics will best permit emergency physicians to provide appropriate sedation and anxiolysis for the frightened, injured children we treat every day.

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