KETAMINE, like many other drugs, was the fruit of investigative labors shared by anesthesiologists and pharmacologists, as recently described by Domino1 in an excellent account of the early years of development and use of this drug. Ketamine was first administered to humans in 1964, and results of that early experience were published in 1965.2 Now on its way to boasting a 50-yr history of clinical utility, ketamine is a candidate for membership in the select club of classic drugs still in good standing, alongside aspirin, morphine, lidocaine, and diazepam. In its mechanism of action, ketamine differs from conventional inhalation and injection anesthetics mainly because it is a noncompetitive antagonist at the N-methyl-D-aspartate receptor.3

Early on, clinicians noted the beneficial effects of ketamine on the respiratory system, observing that central respiratory drive depression was scant; upper airway muscle, pharyngeal, and laryngeal reflexes were preserved; and there was an evident bronchodilator effect. These novel features were surprising, distinguishing a ketamine-induced clinical state from that of other general anesthetics or opioids, as well as from a state of coma. When Corsen and Domino4 recruited healthy volunteers for a 1965 study of the effects of ketamine on the parameters of breathing, they recorded a slight transient decrease in minute volume but maintenance of arterial blood gases. The words of these authors are worth reading today:

“Of particular interest was the observation that protective reflexes—pharyngeal, laryngeal, eyelid, and corneal—were present during the entire course of anesthesia. During surgery inside and around the mouth, there was no need for an endotracheal tube. . . . In some instances the jaw muscles appeared to be more tense.”

In this issue of ANESTHESIOLOGY, Eikermann et al5 contribute to our understanding of the respiratory effects of ketamine on the basis of two carefully conceived, elegant experiments in rats. In the first, they compared the acute effects of administering ketamine and propofol, taking measurements at the median effective dose (ED₅₀) and after administration of doses that were 0.66 of the ED₅₀ and 1.5-fold the ED₅₀. In the second experiment, the authors used chronically instrumented rats (carrying electrodes for genioglossus and neck electromyography, as well as for the recording of a cortical electroencephalogram) to study effects in four situations: in awake and sleep states and after low and high doses of ketamine injected intraperitoneally. Their results confirm that ventilatory depression is scant, and that there is a slight increase in the duty cycle (inspiratory time divided by total respiratory time divided by total respiratory cycle time). However, the most remarkable findings they report are that ketamine increases genioglossus muscle activity while abolishing the coupling between loss of consciousness and upper airway dilator muscle activity. These results can be extrapolated to humans only cautiously, given that the airway effects of anesthetics differ between species. The contraction of the large genioglossus muscle elevates the tongue and pushes it forward, increasing the diameter of the upper airway and decreasing its collapsibility.6,7 Hypotonia causes posterior displacement to a position where the tongue may occlude the pharynx. Thus, electromyography of the genioglossus muscle has been considered an important indication of upper airway patency.

“The findings of Eikermann [and coworkers], that ketamine can be used in spontaneous ventilation and that the airway remains unobstructed, confirm that this anesthetic merits our confidence in its safety profile.”


Accepted for publication October 11, 2011. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Copyright © 2011, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. Anesthesiology 2012; 116:6-8

This Editorial View accompanies the following article: Eikermann M, Grosse-Sundrup M, Zaremba S, Henry ME, Bittner EA, Hofmann U, Chamberlin NL: Ketamine activates breathing and abolishes the coupling between loss of consciousness and upper airway dilator muscle dysfunction. ANESTHESIOLOGY 2012; 116:35-46.
In the decades that have passed between the publication of the article by Corssen and Domino\textsuperscript{4} and this most recent contribution based on animals, we have seen few studies of the upper airway muscle effects of ketamine. In cats, Nishino \textit{et al.}\textsuperscript{8} demonstrated in the 1980s that ketamine activates the adductor muscles to open the larynx. Authors from the same laboratory also showed that although thiopental and diazepam depress hypoglossal nerve activity more than phrenic nerve activity, ketamine affects these nerves similarly.\textsuperscript{9} Thus, ketamine better preserves upper airway patency and muscle activity. Later, Drummond\textsuperscript{10} compared the effects of midazolam and ketamine by placing electrodes on the tongue and neck of human subjects, finding that intravenous ketamine (1 mg/kg) did not cause a significant decrease in tongue muscle activity, in contrast with a 42\% decrease observed after injection of midazolam (5 mg). More recently Saponjic \textit{et al.}\textsuperscript{11} injected ketamine into the pedunculopontine tegmental nucleus of rats, observing patterns that suggest that respiratory rate and muscle tone seem to be glutamate-mediated processes at the \textit{N}-methyl-\textit{D}-aspartate receptors.

However, maintenance of pharyngeal muscle tone and upper airway patency are no guarantee against bronchial aspiration. Most reviews emphasize that ketamine preserves reflexes in the pharynx and larynx, but little research has been done to confirm this. Carson \textit{et al.}\textsuperscript{12} studied laryngeal function indirectly by first instilling a radiopaque contrast medium into the pharynx and then looking for radiographic evidence of aspiration into the tracheobronchial tree after sedation with ketamine and other drugs with or without premedication in obstetric patients. They reported that aspiration to the lung was slight after low doses of ketamine (1 mg/kg) in nonpremedicated patients. However, the saliorrhea that is associated with ketamine administration in the company of maintained laryngeal reflexes can lead to laryngeal spasm when the throat is subjected to mechanical stimulus. When low-dose ketamine has been used in pediatric emergency settings, the incidence of laryngeal and bronchial spasm has been very low.\textsuperscript{13}

The new study by Eikermann \textit{et al.}\textsuperscript{5} raises several questions. One is whether or not the respiratory effects of ketamine are dose-dependent. A dose of approximately 1 mg/kg is perhaps the safest one in humans, but is it adequate for induction and maintenance of anesthesia under normal conditions? It currently is unusual to use ketamine as the only anesthetic outside of critical care conditions, but “low” doses (0.2–0.5 mg/kg) are used increasingly to complement other anesthetics in sedation and analgesia, including the management of chronic pain. Thus, a second question refers to the respiratory effect of these drug combinations and whether or not the patient is safer when ketamine is added. We believe so, but we need studies to confirm that combinations of ketamine and other drugs are safer than single-drug applications. Another question arises in relation to the available pharmaceutical preparations of ketamine. In most studies, including the one of Eikermann \textit{et al.}\textsuperscript{5} in this issue, the racemic form has been used, but we still lack information about the respiratory effects of differing enantiomeric proportions of \textit{S}-ketamine and \textit{R}-ketamine.

In summary, ketamine certainly will never become a first-line anesthetic, but it will keep its place as an excellent complementary drug and will become the subject of more research because of its wide margin of safety in relation to vital functions. A stronger role for ketamine in analgesia and procedural sedation for many diagnostic and therapeutic procedures seems appropriate, in adults as well as in children. The findings of Eikermann \textit{et al.}\textsuperscript{5} that ketamine can be used in spontaneous ventilation and that the airway remains unobstructed, confirm that this anesthetic merits our confidence in its safety profile. Under these circumstances, ketamine has become a reasonable candidate for extended use,\textsuperscript{14} and as we see it increasingly used by non-anesthesiologists for nonsurgical procedures outside the operating room, it is just possible that we may become emboldened in a new debate about how to use this drug appropriately.

\textbf{Jaume Canet, M.D., Ph.D., † Jorge Castillo, M.D., Ph.D.†}

†Department of Anesthesiology and Postoperative Care Unit, Hospital Universitari Germans Trias i Pujol, Barcelona. Spain. jcanet.germanstrias@gencat.cat. †Department of Anesthesiology, Hospital del Mar, Institut Municipal d’Investigació Médica, Universitat Autònoma de Barcelona, Barcelona, Spain.

\textbf{References}

1. Domino EF: Taming the ketamine tiger: 1965. \textit{Anesthesiology} 2010; 113:678–84

ANESTHESIOLOGY REFLECTIONS

Mrs. Winslow’s Soothing Syrup

In Bangor, Maine, locals boast that, after marrying Mayflower descendant Joseph Winslow, Mrs. Charlotte Noyes Winslow (1789–1850) formulated an opiate-laced syrup to soothe the restlessness of her simultaneously teething twin daughters in 1807. A younger sister of those twins would marry a druggist who, with a junior partner, would form “Curtis & Perkins,” the firm that would market “Mrs. Winslow’s Soothing Syrup” (above) from Bangor and then New York to North America and the British Commonwealth. Legislation and then litigation would reduce morphine content per fluid ounce of this 24-proof elixir from its original 65 mg of morphine in the 1830s to 26 and then 0 mg in, respectively, 1911 and 1915. Although branded a “Baby Killer” by the American Medical Association, this nostrum would be sold until the 1930s, more than 80 years after the syrup had, ironically, soothed Mrs. Winslow’s sore throat but failed in curing her terminal case of scarlet fever. (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the Anesthesiology Reflections online collection available at www.anesthesiology.org.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA’s Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.