NEW DRUGS ON THE HORIZON MAY IMPROVE THE QUALITY AND SAFETY OF ANESTHESIA

As a junior dental student at The Ohio State University College of Dentistry, your editor had the rather unique opportunity to provide intravenous moderate sedation for dental phobic patients for restorative dentistry under the supervision of the late Dr N. Wayne Hiatt, an American Dental Society of Anesthesiology past president and Heidbrink Award winner, and another part-time general dentist, Dr Raymond D. Johnston. Although we used a combination of pentobarbital, promethazine, and meperidine, Dr Hiatt had become intrigued in his private practice of general dentistry by a newly-approved intravenous drug called diazepam (Valium). In my senior year, I had the additional opportunity of being able to use this drug with both of these instructors for some of my clinic patients and was able to see firsthand what a marvelous improvement it was over the standard intravenous sedatives that I had used the previous year. Diazepam was a revolutionary advancement in intravenous sedation. It was not just a pharmacological clone of the other sedatives, but represented a whole new class of drug with some major advantages and only minor disadvantages. Many other benzodiazepines have been marketed since then, but they are really all about the same in pharmacologic activity and clinical use, with perhaps a few minor differences among them. For example, although midazolam is now more popular than diazepam, it is not the novel drug that diazepam was when it first was marketed.

Of all the new drugs introduced each year, the vast majority of them are not really novel like diazepam but rather "me-too" drugs, that is, close cousins to other existing drugs in their class with no tremendous advantages over existing drugs other than what the marketing departments of the manufacturers can spin. Although the advent of the cyclooxygenase-2 nonsteroidal anti-inflammatory drugs was thought to represent one of the new breakthrough miracle drugs, the initial enthusiasm about them has waned because of their significant side effects. One could argue that propofol is a new wonder drug because it is not just another refinement of the barbiturate molecule. Although its ultrashort duration of activity is in fact somewhat similar to that of the classic sedative-hypnotics such as thiopental (Pentothal) and methohexital (Brevital), propofol is a wonderful alternative to the barbiturates because of its limited duration of activity that provides for a rapid, clear-headed recovery, even after prolonged infusions, and its antinausea effects.

In this issue of *Anesthesia Progress*, the pharmacokinetics are described of a new drug that hopefully will soon be marketed. Although NV-101 is actually phentolamine, which was marketed for decades as Regitine and used as a vasodilator to treat hypertension and to help diagnose pheochromocytoma, its new indication will be to speed the reversal of the numbing effects of local anesthetics. Its alpha-adrenergic blocking activity promotes vasodilation and antagonizes the vasoconstrictive effects of epinephrine. Phentolamine increases blood flow through the injection site to flush the local anesthetic from the proximity of the nerve. It appears that when the drug is used in this manner, it is safe with minimal side effects. If the manufacturer makes this drug reasonably affordable, NV-101 could be one of those revolutionary drugs that could eliminate one of the most common complaints associated with general dentistry, a numb lip and tongue long after the dental procedure is completed. It will be exciting to see if this drug will eventually be classified as one of those miracle breakthrough drugs that change clinical practice.

Another wonder drug on the immediate horizon, ORG 25969 (sugammadex), is a new type of reversal agent for nondepolarizing neuromuscular blocking drugs (NMBs) such as rocuronium. Unlike anticholinesterase agents such as neostigmine that permit the concentration of acetylcholine to build up in the synaptic cleft of skeletal muscle endplates to push the NMBs from their receptor sites, sugammadex physically encapsulates the molecules of the NMBs like rocuronium so that the blockade disappears much more rapidly and completely, even when the blockade is profound. Sugammadex is a gamma cyclodextrin produced from starch degradation and has the proposed trade name of Bridion. It appears to have essentially no side effects, unlike its counterparts, which produce many unwanted cholinergic muscarinic effects such as hypersalivation, increased gastrointestinal motility, and severe bradycardia. The drug resembles one of the original video arcade games called Pac-Man, in which a little icon with a big mouth and a healthy appetite could be maneuvered around the screen to gobble up the enemy icons. Its future importance is that because it can very rapidly reverse the effects of rocuronium, the duration of action of rocuronium can be made as short as that of succinylcholine. That gives rocuronium, which is normally classified as an intermediate-duration NMB, the potential for becoming an ultrashort-acting NMB soon after its effects are reversed. Thus, rocuronium could be

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used to rapidly treat laryngospasm or to facilitate endotracheal intubation, and then it could be quickly reversed by sugammadex so that spontaneous respiration could resume with minimal delay. With no concerns of the muscle fasciculations, the postanesthetic muscle soreness, and the possibility of triggering malignant hyperthermia that are associated with succinylcholine, the combination of rocuronium followed later by sugammadex could forever replace succinylcholine for managing airway intubation for short cases and laryngospasm. Once sugammadex gets FDA approval and postmarketing studies are completed to give us more clinical experience with it, succinylcholine may finally be put to rest for a job well done but whose time has now passed.

One additional new wonder drug that may have an impact on the safety of local anesthesia is a new use for Intralipid, a fat emulsion primarily used for intravenous nutrition. Its new off-label use is to bind local anesthetic molecules to treat cardiac conduction blockade that develops as a consequence of a local anesthetic overdose. Several case reports have been published in which it has been used successfully to save patients who were unresponsive to the usual resuscitation methods for local anesthetic overdose. All patients completely recovered shortly after intravenous injections of the lipid emulsion, which is essentially the same type of vehicle used in manufacturing some brands of propofol. A website, www.lipidrescue.org, has been established for practitioners to submit case reports of this new emergency use. Intralipid is already being stocked by some anesthesiologists who frequently use maximum recommended doses of local anesthetics in many of their major conduction nerve blocks, particularly in obstetric anesthesia for epidural analgesia and anesthesia in parturients who have a lower threshold for local anesthetic toxicity. Although this drug would likely have little use in most dental offices, dentists with training in intravenous techniques who use large doses of local anesthetics for complex and prolonged procedures may be wise to stock this drug. Additionally, it may become a standard drug for emergency room physicians who might ultimately treat an overdosed patient arriving from an office setting.

Whether or not these new drugs or new indications for older drugs have the same impact on our profession as did Valium when it was first introduced remains to be seen. In the meantime, it is exciting not only to have administered a few novel, practice-changing drugs that were introduced during my career, but also to have given drugs that represent refinements of existing drugs, such as desflurane and sevoflurane, which replaced halothane. It is also exciting that the research scientists continue to discover new drugs and new uses for older drugs that improve the quality and safety of anesthesia.

Joel M. Weaver DDS, PhD
Editor-in-Chief