WHEN CAN A NORMAL DOSE BE AN OVERDOSE? WHO IS AT RISK?

For most drugs, irrespective of their indications or mechanisms of actions, there is a recommended dose for adults and often multiple age- or weight-based recommended doses for children in the US Food and Drug Administration (FDA)-approved labeling, as seen in the package insert. For triazolam (Halcion) the usual recommended adult dose is 0.25 mg. Some drugs also have a recommended dose for elderly, medically compromised, or debilitated patients. For triazolam, this FDA-recommended dose is 0.125 mg. Many drugs also have an FDA maximum recommended dose (MRD) above which either there is insufficient data on safety and efficacy or else there is sufficient data to suggest that administering or prescribing above that limit markedly increases the risk of serious side effects such as overdose toxicity. For triazolam, the FDA's MRD is 0.5 mg. In fact, in the package insert, the FDA warns, "A dose of 0.5 mg should be used only for exceptional patients who do not respond adequately to a trial of a lower dose because the risk of several adverse reactions increases with the size of the dose administered. A dose of 0.5 mg should not be exceeded. In geriatric and/or debilitated patients the recommended dosage range is 0.125 mg to 0.25 mg. Therapy should be initiated at 0.125 mg in these groups, and the 0.25 mg dose should be used only for exceptional patients who do not respond to a trial of the lower dose. A dose of 0.25 mg should not be exceeded in these patients." Although it is true that triazolam is indicated only for short-term insomnia, it is no more or less safe when used off label for procedural sedation at the recommended doses. Depending on the potential severity of the possible toxicity for a selected patient, one could consider giving more than the MRD if needed. However, if subsequent overdose toxicity occurs and causes significant harm, the practitioner may not have sufficient scientific evidence to demonstrate that the decision to use that higher dose was safe, justified, and within the standard of care.

We are all aware of the bell-shaped curve of biological variability, where the response to a dose of a drug can produce only a small effect in some people, a usual effect in most people, and an exaggerated effect in others. Thus, neither the recommended dose nor the MRD is absolutely safe for everyone. The dentist must understand this point and take into consideration all the patient variables that might make the MRD, or even the recommended dose, unsafe. So who are these suscep-

tible patients? Smaller females and children certainly can have exaggerated drug effects from a usual dose. Those with unknown genetic factors that slow drug biotransformation or have altered drug receptors may fit into this category. Patients who have other drugs in their system that are known or sometimes unknown to the dentist can have additive effects. A large number of medically compromised, debilitated, and elderly patients can also exhibit drug toxicity from even small doses.

The unfortunate patient who happens to be supersusceptible to even the usual recommended dose may develop overdose toxicity even though that dose when given to the vast majority of patients would be fine. For example, a normal dose of a drug with sedative properties given to a morbidly obese patient with severe obstructive sleep apnea (OSA) or to a severely debilitated patient can produce unconsciousness, loss of airway, and even apnea during a procedure. Interestingly, drugs with intermediate or long duration of clinical activity can also pose an additional problem once the patient is dismissed for home. This is especially a concern for patients with severe OSA, of whom some have a normal body habitus and many others are morbidly obese. These patients have numerous apneic periods in their sleep due to pharyngeal soft tissue relaxation resulting in airway obstruction that causes their oxygen saturation to drop to life-threatening levels in conjunction with elevated levels of carbon dioxide. These abnormalities then trigger a primitive arousal mechanism that briefly awakens the patient and causes him or her to open the obstructed airway, which allows several breaths to be taken, often just before irreversible brain damage from hypoxic ischemia would otherwise start to occur. With these several breaths, oxygen levels then rise, carbon dioxide levels fall, and the patient again falls asleep, obstructs again, and the cycle repeats itself throughout the night. Any interference with this primitive arousal system by central nervous system depressant drugs such as sedatives, anxiolytics, opioids, and alcohol can be lethal because the obstruction would not be relieved if the patient does not awaken, and ventilation would soon be blocked until the patient dies. Additionally, the continuing elevation of carbon dioxide levels during this prolonged obstructed period also contributes to deeper levels of unconsciousness, because these high levels can have general anesthetic properties.

Residual effects from the drugs still present from the procedural sedation and possibly augmented by opioids prescribed for pain relief can block the arousal mechanism in those with OSA so that the patient does not

awaken, does not open the airway, and does not breathe, and soon death ensues. Although the patient might appear to be only slightly affected by these drugs while awake, once he or she goes to sleep, the insidious depressant effects of the residual drugs combined with OSA can result in a disaster. The drug blood levels of the deceased when measured at autopsy might indicate that the patient was in a subtherapeutic range, but that dose nevertheless was just enough to produce an overdose for that highly susceptible patient.

For the normal-sized dental patient, the maximum recommended dose for lidocaine with 1 : 100,000 epinephrine is 7 mg/kg. A 50-kg healthy teenager therefore could be expected to safely tolerate a dose of 350 mg of the lidocaine, which is the equivalent of almost 10 cartridges of the 2% concentration. However, if a patient previously weighed 120 kg but now has metastatic cancer with significant liver involvement, is severely jaundiced, and now weighs 50 kg, the same 350-mg dose that was safe for the 50-kg teenager is not equally safe for this 50-kg cancer patient needing a full-mouth extraction. Although there are no specific guidelines on how to calculate a safe reduced dosage for severely compromised patients, the dentist is expected to use due caution and perhaps give no more than half of the MRD to avoid a toxic local anesthetic overdose in this patient with reduced serum protein binding capacity and hepatic dysfunction. Thus under this circumstance of severe medical debilitation, an overdose of local anesthetic can occur even within the normal dose range.

When triazolam was originally developed, the FDA approved marketing of a 0.5 mg tablet, but because of postmarketing reports of significant side effects at that dose, the 0.5 mg tablet was eliminated in favor of the lower dosage forms currently available. Similarly, the FDA recently has decreased the MRD for zolpidem (Ambien), a drug for insomnia that is similar to triazolam, although it is in a slightly different class. The FDA has now indicated that the 10-mg dose recommendation should be decreased to 5 mg in women, and the prescriber should consider also dropping the recommended dose to 5 mg in men. In light of recent enteral sedation deaths in dental offices in North Carolina, Hawaii, and earlier in Missouri where overdoses in susceptible patients appear to have occurred, the FDA could issue a black box warning not to administer more than its current MRD for all types of oral drugs used for procedural sedation, especially in patients who suffer from OSA or are otherwise debilitated or elderly.

The bottom line is that elderly, debilitated, and medically compromised patients, including those with diagnosed as well as undiagnosed severe OSA, are at increased risk for dying during procedural sedation and afterwards at home during sleep when sedatives and opioids can still exert their depressant effects on the

central nervous system. To help screen for undiagnosed OSA, the dentist should use the STOP-BANG scoring system questionnaire:

Snoring—loud enough to be heard through closed doors?

Tired—often feel tired, fatigued, or sleepy during daytime?

Observed—has anyone observed you stop breathing during sleep?

Pressure—do you have or are you being treated for high blood pressure?

BMI—more than 35 kg/m² according to BMI [body mass index] chart?

Age—over 50?

Neck—circumference greater than 40 cm?

Gender—male?

High risk of OSA: answering yes to 3 or more items

Low risk of OSA: answering yes to fewer than 3 items

For those with OSA already diagnosed in a sleep study laboratory, its severity is typically graded by the Apnea-Hypopnea Index (AHI) that combines the number of apneic episodes lasting at least 10 seconds and hypopneas per hour of sleep while simultaneously a recording of the lowest pulse oximeter reading is made. The AHI values for the severity of the OSA range from mild (5–15/h) through moderate (15–30/h) and severe (>30/h).

Not all patients are suitable for office sedation at any dose, and a cookbook sedation formula for everyone is likewise a disaster waiting to happen when given to highly susceptible patients. Once a thorough past medical history and an evaluation have been completed by the dentist, augmented when indicated by additional information supplied by the patient's medical team, an appropriate individualized sedation plan may be devised, with safety being the primary objective rather than attaining ideal clinical efficacy where the patient does not move during the dental procedure. A normal dose can definitely be an overdose in highly susceptible people. "Safety first" must be our motto.

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