Chapter 8

Anxiolysis for Oral Surgery and Other Dental Procedures

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Introduction

This chapter discusses the need for sedation, the risks of various modalities of sedation, techniques to minimize the risks, and two safe techniques to control fear and apprehension in the dental office. The biggest risk of sedation is respiratory depression. Mechanisms of respiratory control will be reviewed, and various forms of monitoring will be discussed along with respiratory conditions that complicate sedations. Nitrous oxide/oxygen sedation are covered, as are oral sedatives—with emphasis on benzodiazepines and specifically the use of triazolam (Halcion) for conscious sedation to control fear and apprehensive.

Oral surgery is somewhat traumatic for all patients. Because of this, many oral surgeons will suggest deep intravenous (IV) sedation/general anesthesia for even simple surgery procedures. Most of the in-office surgery procedures can be done with local anesthesia; however, many patients prefer some form of sedation for their surgery. The surgery is easier and faster for the surgeon if the patient is comfortable. The use of nitrous oxide/oxygen sedation with and without oral triazolam are discussed. With these two drugs, almost all surgery procedures can be completed on even quite fearful patients without the need for the more hazardous general anesthesia.

A second issue is the dental patient who is a dental phobic. A *USA Today* article quoted American Dental Association (ADA) figures detailing that 12 million Americans are dental phobics. Another source estimated that 12 to 24 million suffer dental anxiety.[1] Coping with the difficult-to-manage fearful patient has long plagued the profession, and one of the major challenges of dentistry is apprehension control. Fear and pain control are closely related. Fear of future treatment is often the result of lack of pain control in past appointments. Pain control is most often achieved with local anesthesia. According to Weinstein,[2] patients report the incidence of failure of the local anesthetic injection to be as high as 26.4 percent. It is suggested that fear has a high correlation with those who have anesthetic-related problems.[3]

About half the U.S. population avoids yearly dental care. Between 6 and 14 percent

of patients avoid **any** treatment whatsoever because of fear. This phenomenon is not unique to the United States. Others have shown similar problems in Sweden and Japan.[4–6]

Government regulations that dictate who can and cannot be hospitalized (Medicare, Medicaid) and the threat of litigation have caused many dentists to avoid providing dental treatment on all but the most cooperative and easily managed patients. Some dentists refuse to see those patients unable to receive dental care in the usual manner.[7]

In the late 1990s and early 2000s the greatest barrier to using sedation has become dental politics. The target is primarily oral sedation and those practitioners who provide this service. The American Dental Association's committee H proposed guidelines that were passed by the ADA House of Delegates in 2004, severely limiting the use of oral sedatives. Many states' licensing bodies have started adopting these guidelines. The American Association of Oral and Maxillofacial Surgeons has encouraged state licensing boards to limit the use of oral sedation. In one letter sent to state boards, they suggested that the use of oral sedation should have the same certification required of IV sedation.

In this chapter, considerable space is spent referring to the patient who is unconscious, asleep, dozing, and napping—and explaining why I am not comfortable with such a patient. On the other hand, the patient who is orally sedated but awake and will respond to verbal directions is a safe patient. So long as this patient remains conscious, the operator can relax and enjoy performing dentistry. With a proper preoperative evaluation, careful use of the right drug and calculation of its dose, a dentist should never have a patient lose consciousness; that is, "go to sleep." Should this occur, all else should cease until the patient is again verbally responsive or awake. Some states have regulations dictating dentist training and equipment for treating patients receiving general anesthesia, and rightfully so. It is a little late to start buying equipment and getting training when a patient is unconscious. General dentists administering oral conscious sedation need training and special equipment.

As we discuss triazolam, it will become obvious that the chance of problems arising with this drug, when it is used properly, is very slight. But even if complications should occur, with the availability of a selective reversal agent, flumazenil (Romazicon), we reverse the effect that is going beyond the levels we wanted. As you will see later, flumazenil is reported to rapidly reverse the sedation of benzodiazepine drugs, much as naloxone (Narcan) does the opiate drugs.

Various forms of oral sedation have been used by dentists to help apprehensive patients. Patient comfort can be achieved by the practitioner who uses oral sedation, and/or nitrous oxide to allay patient's anxiety and apprehension. Anxiolysis (a relief of anxiety) also decreases the likelihood of stress-induced medical emergencies. The difficulty of using oral agents is the time it takes to get an effect. Since these drugs must be swallowed and absorbed via the small intestine it often takes over an hour to get the drugs into the circulation and see the maximum effect.

What Are the Levels of Sedation?

Sedation needs to be matched to the level of apprehension along with the physical and mental stimulation the patient will have to endure while their dentistry is being provided. Apprehension control is a continuum of the levels of sedation—from no sedation through general anesthesia. A patient with minimal apprehension and a short simple procedure will need less help than a severely phobic patient who will be undergoing a painful, lengthy, noisy, stressful procedure. The levels have been named anxiolysis, moderate sedation/analgesia, deep sedation, and general anesthesia.

Anxiolysis is a drug-induced state during which the patient responds normally to verbal commands. Their cognitive functions and coordination may be impaired, but ventilatory and cardiovascular functions are normal. This level could be compared to a glass or two of wine. These patients are exposed to little, if any, risk. Anxiolysis may be protective for patients with mild to moderate medical conditions that can worsen due to the stress of dentistry. This level of sedation is achieved with light oral sedation and/or nitrous oxide/oxygen sedation.

Moderate sedation/analgesia is a bit deeper; the patient will respond to verbal commands, but you might have to add light tactile stimulation to get a response. They are able to maintain their airway, and spontaneous ventilation is adequate. Their cardiovascular system is normal. This level of sedation is most often achieved with an oral sedative, but light IV sedation could also achieve these levels.

Deep sedation/analgesia takes a patient to a level where they respond only after repeated or painful stimulation. They may not be able to maintain their airway and may need an assist to maintain adequate ventilation. This level requires advanced training for the practitioner, as protective reflexes are now obtunded or absent. Cardiovascular function is maintained.

General anesthesia is a complete loss of consciousness. Often patients will need help to maintain their airway, and their respiratory function may need assistance. They will have lost the protective swallowing, gag, and laryngeal reflexes. General anesthesia can be achieved by the inhalation of potent anesthetics, with IV drugs, with oral drugs if high enough doses are given, or a combination of these. It is imperative if this level is achieved that the practitioner is capable of monitoring the patient's vital signs, maintaining the airway, assisting respiration if necessary, and handling all the various life-threatening emergencies that can occur. Children are much more difficult because they are less forgiving of alterations from normal. Their respiratory physiology has a narrower margin of safety (see Figure 8.1).

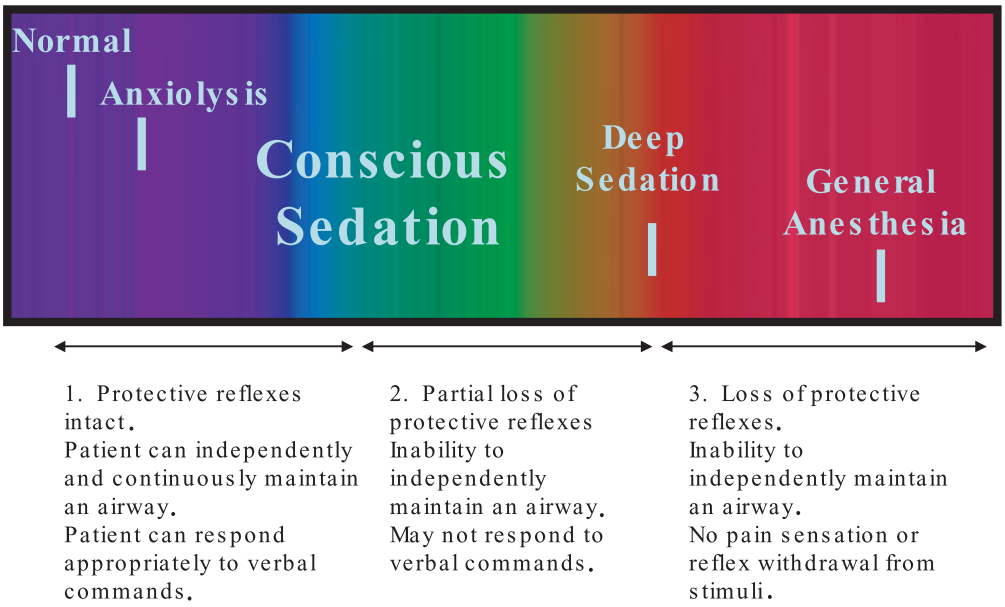

Figure 8-1. This chapter will discuss only area 1 of the spectrum of anesthesia. Areas 2 and 3 require advanced training and come with greater risk to the patient.

How Safe Is Sedation?

Dentists with proper training can perform oral sedation safely and effectively. Most dental therapy can be accomplished on phobic patients using local anesthesia and sedation. Therefore, adequate use of local anesthesia must be considered as the first step of not only pain control but also anxiety control. Many central nervous system (CNS) depressants can alter the level of consciousness. Most of these can produce a hypnotic state if given in higher doses, but only a select few can actually produce a complete state of general anesthesia.

The potential for complications is not limited to the general anesthetic state. It may accompany any degree of drug-induced CNS depression. Respiratory and cardiovascular depression are the most feared complications. Respiratory depression represents the principal negative variable introduced with conscious sedation and, left unrecognized and untreated, is the cause of most serious complications.

Further complicating the question, "To Sedate or Not To Sedate?" is the fact that nearly all dentistry is elective. It is very rare to face the situation in which a life will be lost if treatment is not initiated. A nerve may die; a tooth may be lost; all the teeth may be lost; but the patient will still be alive and reasonably healthy. It is very difficult to accept a dental procedure where there is even a slight risk of death. This is not to say that there is not a very slight risk with even the most simple procedures. Even administration of local anesthesia has resulted in death. But, whatever we do, safety protocol is of the utmost importance (see Figure 8.2).

Sedation and deep sedation/general anesthesia has a remarkable safety record; however, there have been studies showing that the deeper the sedation, particularly when administered to medically compromised patients such as the very young and the elderly, the greater the risk. Dionne reported that overall mortality in the United States associated with general anesthesia, based on self-

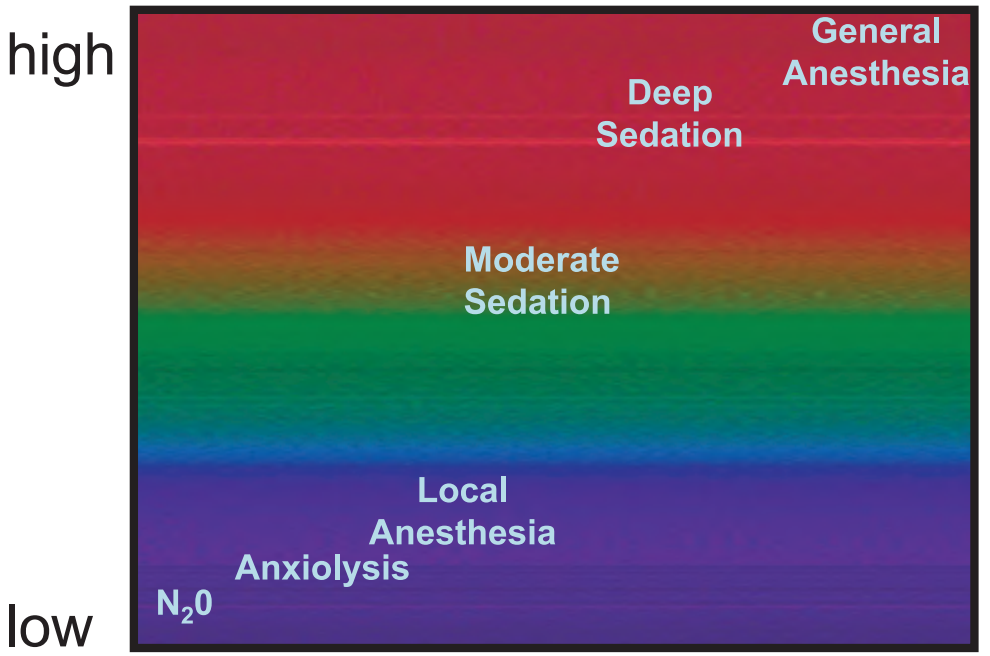

Figure 8-2. The relative risks of various forms of sedation anesthesia. Because of the high levels of oxygen, nitrous oxide is protective for almost all patients. Anxiolysis with oral sedation of a benzodiazepine drug is nearly as safe. With help from Dr. Mark Donaldson B.Sc., Pharm.D.

report of oral surgeons, has ranged from 1:740,000 to 1:349,000; however, self-reporting is usually given little credence because not all cases are acknowledged. A more credible study came out of records from the United Kingdom, where the overall mortality risk was 1:248,000 for general anesthesia and 1:1,000,000 for conscious sedation. Only very low risk could be determined for local anesthesia.[8]

The risk of sedation and anesthesia can be dramatically decreased with modern monitoring devices and the use of persons trained in monitoring and administrating anesthesia. It has been shown that the risk of anesthesia is dramatically reduced when a separate practitioner trained in general anesthesia administers and controls the sedation/anesthesia. In the case of two-operator administered anesthesia, the risk went from 1:248,000 to 1:598,000.[9] This is particularly true when treating patients with underlying medical problems.

Patient Ambulation

A problem that was unique to dentistry but is now affecting our medical colleagues who use day surgery is the need for rapid ambulation. We need to get our patients back to a state that allows them to leave the office in a timely manner. Their reflexes need to be such that they can walk unassisted after a short period of time, even though this author insists that another adult take their arm for additional support. It may be wise to use a wheelchair to transport the patient from the dental chair to their auto. They should not drive, undertake any task that might be hazardous, be placed in a position of responsibility (for example, taking care of children), or make important decisions. Even climbing stairs should be avoided. They need to be accompanied and supervised by a responsible adult for the rest of the day, during which time their activities should be very limited. Operating the remote control of a television is about as complex a cognitive activity as they should attempt. It should be stressed to the patient that although they might feel normal, their reflexes could still be depressed. They need to take the remainder of the day off.

It should be mentioned that some of the benzodiazepine drugs are initially bound to plasma proteins. This binding tends to reverse about six hours after administration. This phenomenon is known as a "second peak effect."[10] When using most benzodiazepines, it is necessary to inform our patients that they will experience an increase in sedation about 5–8 hours after leaving the office. Interestingly, even after this time, blood concentrations of active drug have been reported to be close to 50 percent of what they were during sedation. For this reason, it is imperative that they not undertake any activity requiring cognitive or coordination skills the rest of the day. Because of the long half-life of diazepam (Valium), some practitioners have felt there was reason for some concern even the next day.

Drug Selection

Our choice of drugs is guided by consideration of elimination half-lives and side effects. When we examine sedative systems, we find a continuum of effects from slightly noticeable changes through more profound sedation to general anesthesia, eventually leading to death, if enough drug is administered. "General anesthesia is less safe than conscious sedation, which is less safe than local anesthesia."[11]

It is our goal to choose a sedation system with a very wide difference between desired effect and death in a very broad range of patients. It is ideal if the effects of the drugs can be reversed at will if our system seems to be getting out of control.

It is also our goal to create a state of tranquility that will allow the patient to comfortably undergo the needed procedure. If we

can alleviate apprehension without changing any of the patient's other parameters, we have achieved success. In fact, we always cause some change in our patients' physiology; however, with modern drugs these changes are much less hazardous than what was accepted a few years ago.

Routes of Drug Administration

In attempting to create a state of tranquility, we must get a certain concentration of agent to the appropriate location in the central nervous system. When considering routes, we should consider patient comfort, time to achieve effect, control of the effect, ease of administration, the skill needed for administration of the drug, necessary equipment for administration, and monitoring of the patient. Unfortunately, we must also consider medical-legal questions of insurance and regulation by governmental organizations.

In general, the faster the drug reaches the CNS and has an effect, the better the control we have over the sedation. By titrating for effect, we can give just that amount of drug that is necessary to control apprehension. Both intravenous and inhalation agents can be readily controlled in this manner. Other routes of administration require administering an appropriate dose and waiting up to an hour to see the desired effect. These routes require very specific dosages, usually associated with body size. They require conservative dosages, as hypersensitivity to a medication will not be obvious until it is much too late to adjust the dosage. It is imperative that a drug with a very wide range of safety be used when these slower routes of uptake are utilized. Ideally, we will have reversal agents that can deactivate the drug in the case of overdose when using these routes.

We, in dentistry, have used and continue to use a variety of agents and combinations of agents. Multiple agents often complicate the treatment, as each has side effects that can be additive. They all are CNS depressants and some have unwanted depressing effects on respiratory and the cardiovascular systems. The combination of all these effects can lead to problems that are hard to predict and even more difficult to control and treat. However, if only one agent is used, the side effects are often more predictable and more treatable.

It is easier and safer to use a single agent, as we then only have one set of side effects. This assumes a single agent will provide the needed result at a concentration where few side effects are present. When Dionne looked at drug mixtures used by 264 dentists, he found 82 distinct combinations.[12] He said, "The scientific basis for the use of such a diverse group of agents and combinations is unclear."[13]

Inhalation Sedation

The inhalation route of administration offers a major advantage when we consider an overdose. By removing the source of the drug (having the patient breathe room air or 100 percent oxygen), the patient will excrete most inhalation agents via the lungs, thus reversing the overdose.

Oral Sedation

Several factors come to light when we consider oral sedatives. The time from ingestion to sedation becomes very important. For any effect to take place, the drug must be absorbed into the bloodstream and delivered to the site of action, usually thought to be in the central nervous system, in sufficient quantities to be effective. Some drugs can be absorbed sublingually; others must be swallowed and absorbed from the small intestine. Depending on the time necessary for absorption, it might be necessary to have the patient take the drug at home before coming to the office. This author prefers to administer the drug in the office because then you know how much was taken, when

it was taken, and by whom it was taken. You don't have to worry about the patient trying to drive to the appointment as the drug starts to take effect, and should there be a reaction to the drug, the patient is in the office where aid can be administered.

One downside is that because it will take 45 minutes to one hour to get the desired sedation, it is time-consuming to titrate or alter the dose if a patient is not adequately sedated.

Intravenous Sedation

With the regulations that are now in place in many states, it is nearly impossible for the average general dentist to use intravenous sedation. Many states require a 60-hour course with 20 patient sedations in addition to any training that was received in dental school. Intravenous sedation has several advantages, however. When giving a drug IV, one slowly titrates the amount to the level of sedation desired. For most drugs, these effects began to diminish in a short period of time—first, due to redistribution to other tissues in the body (primarily fat stores), and then more slowly as the drug is metabolized into inactive forms or eliminated in the urine or feces.

Although this should be the safest route of administration, it is possible to go from conscious to deep general anesthesia in a matter of seconds. Although this should be a very safe technique, this is where we are seeing deaths.

Drug Options

Historically, many drugs and routes of administration have been used to control apprehension in dental offices. As stated earlier, insurance companies, state regulatory bodies, and other entities have all but eliminated intravenous sedation from the armamentarium of general dentists. If we look into other methods of sedation, however, we will see that all is not lost for the phobic patient.

Nitrous Oxide

Nitrous oxide is possibly the safest of all sedatives. It is estimated that close to 40 percent of dentists are equipped to administer nitrous oxide. It has been used in dentistry for more than 150 years. Trace nitrous oxide released into the air of the dental office, and its effect on the dental staff, however, must be considered. It is recommended that there be postoperative oxygenation for not only nitrous oxide but also other sedatives. If one is looking for a very safe anxiolytic drug from which the patient recovers quickly and with which the patient is able to drive to and from the office, nitrous oxide is the only choice.

Alcohol

Alcohol has been used by some patients for years to help with their dental treatments. It is not unusual for a patient to self-medicate with a bit of liquid reinforcement before coming to an appointment. **It is important when considering the use of sedatives for apprehension control that patients be warned against using any other substance that is a central nervous system depressant**. The combination of benzodiazepines and alcohol has lead to very serious respiratory depression and death.

Chloral Hydrate

This drug has been a favorite, particularly for children. Evidence is emerging, however, that indicates it may not be as safe as we believed. Chloral hydrate's sedative action comes from its metabolite, trichloroethanol. The peak activity occurs in the plasma within 20 to 60 minutes after oral administration. Its half-life is 4–12 hours. It acts primarily on the CNS and has little effect on the respiratory and cardiovascular systems of healthy patients.

In higher doses, chloral hydrate becomes a cardiac irritant. There have been several reported cases of overdose leading to hypotension. In one report of two patients, when this hypotension was treated with catecholamines or agents that released catecholamines, both patients experienced cardiac arrest; one survived, the other did not. Any other CNS depressant will enhance the sedation-depression of chloral hydrate, including nitrous oxide and narcotics.[14] Deaths have occurred in combination with local anesthetics when used with small children. It is thought that often this is due to using a toxic dose of local anesthesia: four cartridges—one for each quadrant to be treated. Even two cartridges of local anesthesia can be a toxic dose for small children.

Barbiturates

Barbiturates were the standard antianxiety agent for both medical and dental patients for many years. Barbiturates make a patient drowsy, and sleepy patients tend to be less apprehensive. In larger doses, barbiturates have the potential to render patients asleep. It is in this way that the short- and ultrashort-acting barbiturates were used as induction agents for general anesthesia and for very brief general anesthetics.

The ratio of the dose necessary for sleep and the dose that will end in death—the **therapeutic index**—is usually stated to be a factor of two, as compared to diazepam, with a ratio of 20.[15] Unfortunately, barbiturate drugs in higher doses tend to be potent cardiac and respiratory depressants. Because of their addictive nature, they are not administered for long-term anxiety control.[16]

Benzodiazepines

Benzodiazepine (BZD) drugs come in many varieties. They differ in the rapidity that they take effect, the time it takes for them to wear off, time to peak blood levels, and half-lives. While the names are different they are more similar than different in their effect (beyond uptake and deactivation times). Dentistry has several BZDs that are ideal for use with apprehensive patients, and the effect can be tailored to the time necessary to perform the procedures being contemplated. One, triazolam, is well suited to dentistry. Triazolam came to market as a sleep aid and has become very popular and controversial. Triazolam will be discussed in detail.

The Two Most Useful Sedative Drugs for the General Dentist

Nitrous oxide has an interesting history. Originally it was used as an attraction at public science shows. It was at such a program that a dentist, Horris Wells, saw a participant in a nitrous frolic receive a serious injury causing a dramatic wound . . . with no pain. He took this knowledge to his office and began offering painless dentistry using nitrous oxide as a general anesthetic.

Its history as a general anesthetic has brought dentistry some criticism. Nitrous oxide is a weak anesthetic agent. At one atmosphere of pressure, 80 percent nitrous oxide is usually considered to be the minimum concentration that will achieve general anesthesia. Even at this concentration, it is not possible to render some patients unconscious. If we go to a higher concentration, we begin to encroach on the 21 percent oxygen found in the atmosphere and expose our patients to hypoxia.

The standard of the past was to watch the patient's color. When they began to show a blue tinge of cyanosis, the procedure was started. (I like to state, tongue in cheek, that dentists hoped the pain of the extraction would restart the heart.) Anesthetics were very short. One tooth in the forceps, one in the air and one hitting the bucket, simultaneously, was the goal. Actually, many general anesthetics were done by this technique with an amazing safety record, which may be

more testimony to a patient's desire to live than to the safety of the procedure. Today, this hypoxic anesthesia technique would be severely criticized, as it should be.

Because nitrous oxide is absorbed and removed from the blood stream via the lungs essentially unchanged, nitrous oxide is a very safe sedative. But its major disadvantage—its relative weakness—is also its major advantage. Although sedation with nitrous oxide is not adequate for our severely phobic patients because it is such a weak anesthetic agent, there is little risk of sedation rendering the patient unconscious—that is, in a state of general anesthesia. However, it is not impossible. I have had two patients in 40 years who were under general anesthesia with very modest concentrations (less than 40 percent) nitrous oxide. Neither had taken any other drugs. If the patient is not responding even at low concentrations this might be the problem. The mask should be removed and the patient allowed to breathe room air or just oxygen.

Our primary concern in anesthesia is the loss of swallowing and laryngeal reflexes that can lead to regurgitation of stomach contents and aspiration of the low-pH stomach contents into the lungs. So long as a 50 percent concentration of nitrous oxide is not exceeded, there is little chance of general anesthesia or other complications.

The complications that may arise are not serious ones. Occasional vomiting may be seen, but since our patients are always conscious, this is not serious, as protective laryngeal reflexes are present. The patient is definitely uncomfortable, and vomiting certainly can be messy, but it is usually not life-threatening.

Patients will occasionally hallucinate with nitrous. Again, this can be uncomfortable for them. Treatment consists of removing the source of nitrous oxide and reassuring the patient, typically by telling them they are all right and will return to normal in a few minutes. It is helpful to repeatedly assure the patient until the hallucination is over. Use their first name and remind them they are in the dental office—that they should relax and will be back to normal in a few minutes.

Another potential problem deserves mention—that of sexual aberrations. A certain number of female patients will experience sexual feelings while on nitrous oxide.[17] This can happen at relatively low concentrations. Some patients describe the sensation of a sexual orgasm. It is not all that easy to identify when this is taking place. However, if it looks like a duck, walks like a duck, and quacks like a duck, the chances are we are observing a duck. This may, in fact, be the ultimate distraction to dental treatment. Fortunately, it is very rare. For this reason it is important that a male dentist, hygienist, or assistant always be accompanied by a female dental assistant when treating female patients with nitrous oxide. This phenomenon has never been documented in male patients.

A potentially more serious problem can arise if we treat chronic obstructive pulmonary disease (COPD) patients with nitrous oxide. Should a patient be overdosed with nitrous oxide, it is a simple matter to remove the source of the gas, and provided the patient is breathing, they will eliminate the excessive concentration of nitrous oxide. If they are not breathing, we should be ready and able to assist their respiration. This would be a very unusual complication and probably would suggest the patient had other sedatives or was given excessive nitrous oxide (greater than 80 percent). It should be stressed that nitrous oxide is a very safe sedative for almost all patients, provided equipment has been properly installed and maintained.

Nitrous Usage

It is estimated that about 50 percent of dentists have the equipment to administer this mix and that more than 424,000 dental per-

sonnel are exposed to the trace amounts of gas as a result of its administration.[18]

Many dental and dental hygiene schools now take a very cautious attitude toward the use of nitrous oxide. This has come about because of the publication of a number of papers concerned with the effect of waste gases on office personnel, particularly those who are pregnant.

The first indication that anesthetic gases might be a problem for humans was a report in 1967 by Vaisman, who studied Russian female anesthesiologists and reported that 18 of 31 pregnancies ended in spontaneous abortion.[19] Studies have shown similar problems in U.S. operating rooms.[20] It was clear the operating room had the potential to be a hazardous place to work, but it was not clear which chemicals were the causative agents.

Animal Studies

Potent anesthetic agents have been shown to have teratogenic effects in animal studies. Because nitrous oxide was part of many anesthetic administrations, it needed to be evaluated. Many studies showed problems for animals exposed to high levels of nitrous oxide.[21–31] It was shown that nitrous oxide decreases vitamin B_{12}, which can impair DNA synthesis.[32] These studies hint that if the levels are kept low enough the problems can be lessened.

Retroactive Human Studies

The dental office was an ideal study site as there were two types of offices, those that used nitrous oxide and those that did not. Cowen did two such studies in conjunction with the American Dental Association. These studies suggested there is a problem with higher levels of exposure for pregnant staff.[33, 34] Although there may be some problems with these retrospective studies,[35] they did point to a concern for females who were pregnant and working in dental offices where nitrous oxide was used. The studies did not suggest at which level exposure became a problem.

Occupational Hygiene Agencies

There are three governmental bodies associated with setting appropriate levels of exposure to chemicals: OSHA, NIOSH, and ACGIH.[36] The NIOSH publication, *Alert*, suggests the recommended exposure limit (REL) of 25 parts per million (ppm) on a time-weighted average (TWA) of 25-ppm. These levels were recommended after reviewing two studies by Bruce.[37, 38]

The Problem Studies

The TWA level of 25-ppm came from two studies done by Bruce, Bach, and Arbit. In the first study, a difference was shown when subjects were exposed to 50-ppm nitrous oxide with 1-ppm halothane but not to 500-ppm nitrous oxide, except for a digit span test.[39] The second study showed a slight effect to subjects exposed to 500-ppm nitrous oxide for four hours.[40] Note that Bruce recanted this study as flawed in two letters—one in 1983 the other in 1991. He stated,

> "Several years later, we learned that most of the subjects we studied were a unique population that used no mood altering substances and as such, might have been abnormally sensitive to depressant drugs such as nitrous oxide and halothane. There is no longer any need to refer to our conclusions as 'controversial.' They were wrong, derived from data subject to inadvertent sampling bias and not applicable to the general population. The NIOSH standards should be revised".[41,42]

Many papers have been published in the dental literature that mention the motor skill effect, which was not shown for just nitrous

oxide in either study. These two studies and the publications of NIOSH that arose from these studies have been referenced in so many dental journals they have become fact, ignoring the two retraction letters. After a paper is published, it is very nearly impossible to retract the paper.

What Is a Safe Level of Exposure?

What studies have been done with humans that suggest appropriate exposure levels? Ahlborg showed Swedish midwives exposed to nitrous oxide and shift work had no difficulty getting pregnant unless they used nitrous oxide 30 or more times a month to assist with deliveries.[43] In another study of midwives, he showed no increase in spontaneous abortions with exposure to nitrous oxide, but he saw an increase with night shifts, high work loads, and no nitrous.[44] Sweeney performed a study on 20 practicing dentists. The exposures ranged from 50 ppm to more than 5,000 ppm on a time-weighted average. The only depression seen was in three dentists with exposure of more than 1,800 ppm. To set levels that would ensure safety, Sweeney suggested we should not exceed 450 ppm on an 8-hour.[45, 46]

Rowland looked at the ability of female dental assistants to become pregnant (fecundability). He showed no problems if scavenging was used.[47] These two studies strongly suggest that if we use scavenging and keep levels below 450 ppm, the dental office staff is at no risk.

What Levels of Exposure Can Be Achieved?

Early studies showed that the Brown mask, a mask within a mask with suction, could achieve levels of 50 ppm under ideal settings. OSHA reviewed these data and suggested that since this was achievable, it should be our goal. Donaldson has shown that many scavenging devices being used in practicing dental offices can achieve levels in the 40 to 60 ppm range.[48]

How Can Levels Be Controlled?

It is clear that offices should have one of the available scavenging systems on each nitrous oxide/oxygen unit. Today's scavenging systems are predominantly systems with suction placed on the mask over the pop-off valve. Some systems attempt to suck up additional air that is around the mask, and they may remove traces of nitrous oxide that the patient exhaled through their mouth or that leaked from around the mask.

Every nitrous machine must have a scavenging system with adequate suction. There should be a reasonable exchange of air in our dental offices. Outside air should be brought into the office by our heating and cooling systems. It is suggested that the minimum air exchange is five changes per hour, although is it recognized that 15 to 20 changes per hour is better. Hoses and connectors should be checked for leaks. Masks should be selected that fit the patient, and the patient should be discouraged from speaking while receiving nitrous oxide sedation. If all these suggestions are followed, it is possible to stay in the 50-ppm range[49]—well below the 450-ppm exposure level suggested by several authors.

Oxygenation after Nitrous Oxide Oxygen

Oxygen is the one drug that should be available in all dental offices. Oxygen can be used with little regard for side effects or other problems and should be available in every office as part of the emergency protocol. There are exceptions to this generality and times when it should not be used. For example, oxygen should be used cautiously for COPD patients (severe emphysema). If a COPD patient's disease has progressed to its

final stages, his or her breathing may be on an oxygen drive—not the primary carbon dioxide drive. Giving high levels of oxygen to one of these patients could cause him or her to go into respiratory arrest. These patients are normally quite easy to identify because of their obvious respiratory difficulty.

Oxygen is routinely administered after general anesthesia when nitrous oxide was used in order to avoid diffusion hypoxia. This phenomenon was first described by Fink to explain a transient hypoxia after anesthesia in conjunction with nitrous oxide.[50] Nitrous oxide would diffuse out of the blood and fill the alveoli of the lungs and the rest of the respiratory tree. Nitrous oxide crosses from the blood to the alveoli of the lung much more quickly than either oxygen or nitrogen, and thus, nitrous oxide would tend to fill the dead space in the lungs. On the first inspiration of room air, the patient would have a mixture of nitrous oxide from the dead space (150cc of 100 percent nitrous oxide) and 350cc of room air. In theory, this would result in hypoxia that could be a problem for a sick patient, a patient with a compromised respiratory system, or a patient with respiratory depression due to the anesthesia drugs. In the case of general anesthesia, this could be a serious issue.

What is the harm in using some oxygen? Nothing, unless the two gas lines have been switched. In such a case, although the machine reads 100 percent oxygen, it is in reality delivering 100 percent nitrous oxide. There are many ways this can happen. One case occurred in a surgery practice using general anesthesia and resulted in the death of a young, healthy, adult patient.

You can use a pulse oximeter to investigate the need for oxygen after nitrous oxide/oxygen administration. One study failed to show any drop in oxygen saturation if the mask was simply removed at the end of the appointment where nitrous oxide had been used.[51] The study has now been repeated by others with the same results.[52, 53]

An overriding reason for leaving a patient on oxygen, however, is to scavenge the gas the patient is exhaling. With our present knowledge of the risks of trace contaminants of nitrous oxide, we believe we should leave our patients on 100-percent oxygen for five minutes to ensure that the nitrous oxygen they exhale is removed from the atmosphere we breathe. However, if a patient ever becomes unresponsive while on 100-percent oxygen, remove the mask. It may be that the gases have been switched.

Respiratory Effects of Drugs Used for Sedation

Sedation can be performed safely and effectively by dentists with proper training. Respiratory depression is the principal concern when sedation is administered. If we are going to get into trouble, the most likely cause will be due to respiratory depression or respiratory inadequacy due to airway obstruction.

In all cases of dental sedation, patients should remain awake. If the patient tends to fall asleep, they should be awakened. General anesthesia has been described as great amounts of boredom occasionally dispersed with moments of stark terror. Unless you are well equipped, well trained, and certified, you do not want patients to be unconscious. It is not possible to tell napping, dozing, or sleep from general anesthesia without trying to wake the person. If the patient awakes, keep them awake. If they do not awaken, you are not doing conscious sedation. The patient is under general anesthesia. If the patient is not awake, you need to reverse the sedation.

With some drugs, our concern may be that we have depressed the respiration to the point that an adequate exchange of gas is not taking place. The presence of an open airway should be established, evaluation of the level of respiration assessed, and vital signs should be taken. It should be noted that several

studies have shown that watching the chest and/or reservoir bag move is not adequate to ensure an adequate minute volume. Skin color has been relied on in the past as a way of ensuring adequate tissue profusion. The arterial oxygen level can be dangerously low, however, before we see the blue tinge of cyanosis. Cyanosis is no longer considered to be an adequate monitor of arterial oxygen levels. A pulse oximeter and/or capnograph are invaluable in assessing the adequacy of ventilation (see Figures 8.3 and 8.4).

Physiologic Basis of Ventilation

To properly appreciate the importance of monitoring respiration along with reviewing the respiratory advantages of benzodiazepine drugs, we need to review a topic we all studied in dental school but most likely have not thought about since then—respiratory physiology. This is not intended to be a complete discussion. Yet, it will review a minimal level of knowledge that we should have when using sedative drugs.

Our breathing is controlled by several mechanisms. When we consciously take a breath, we have conscious control. Normally, though, our breathing rate and depth are stimulated by carbon dioxide (CO_2), a by-product of our metabolism. CO_2 alters the hydrogen ion concentration, or the pH of our blood. This pH change is the primary stimulus to breathing (see Figure 8.5). Breathing is also stimulated, to a lesser extent, by low concentrations of oxygen. Many drugs affect the CO_2 drive, but nitrous oxide depresses the secondary drive because of a lower oxygen level (see Figure 8.6).

The solution to the aforementioned problems lies in several areas. We should use drugs that minimally depress respiration. Avoid combinations of different drugs that affect several things at once. Monitor the

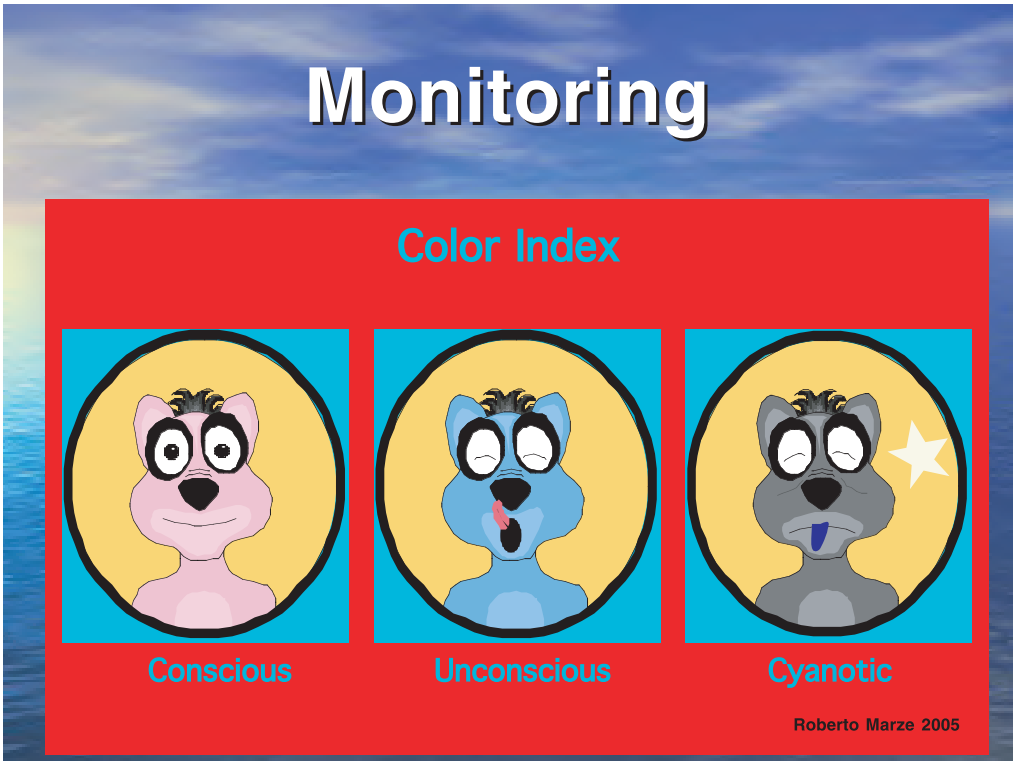

Figure 8-3. Early dental anesthesia with nitrous oxide was monitored by the patient's color. Pink was awake. Slight cyanosis was time to do the extractions. Deep cyanosis was time to give oxygen.

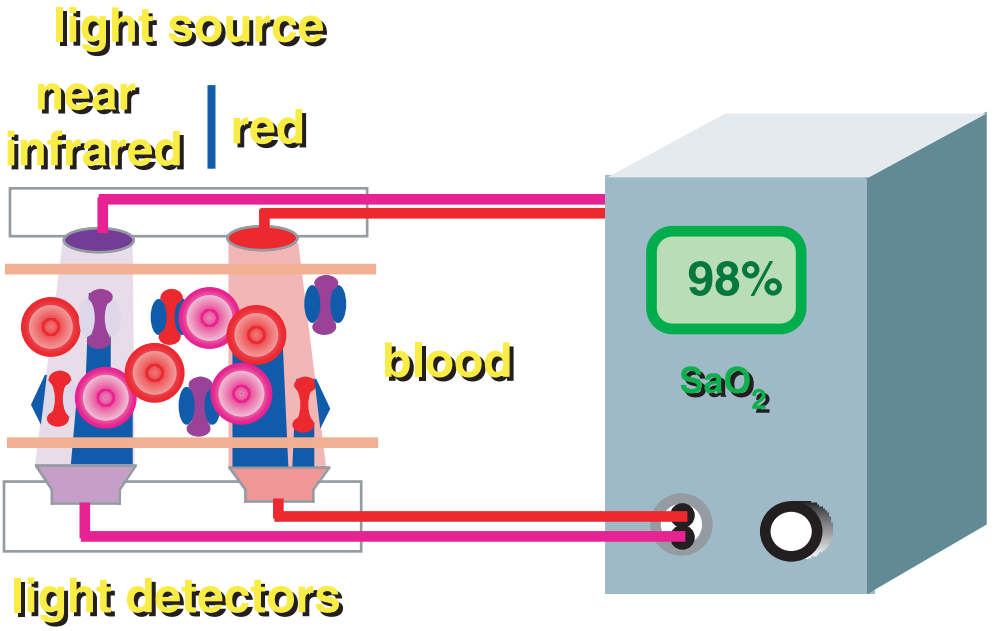

Figure 8-4. A pulse oximeter shines light through tissue, usually a finger. Receptors read the levels of each light. This information is analyzed, and the percentage of oxygen saturation is displayed on the monitor.

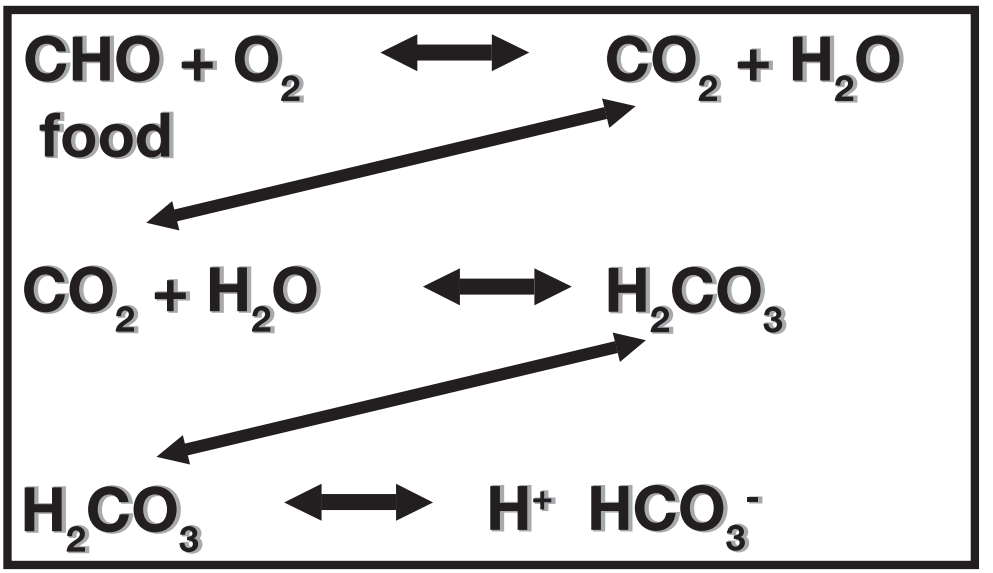

Figure 8-5. Food is oxidized in our bodies and becomes CO_2 and water. The CO_2 is absorbed in the water of the plasma to become carbonic acid. Carbonic acid disassociates into hydrogen ions and bicarbonate ions. The negative log of the hydrogen ion concentration is known as pH. The hydrogen ion is the prime stimulus to respiration. In the COPD patient, bicarbonate ions are absorbed by the kidneys, forcing the hydrogen ions back to carbonic acid. In this way, the stimulation of the hydrogen ion is blunted, forcing them to breathe on oxygen drive. The oxygen drive is depressed by nitrous oxide. High levels of O_2 can do the same.

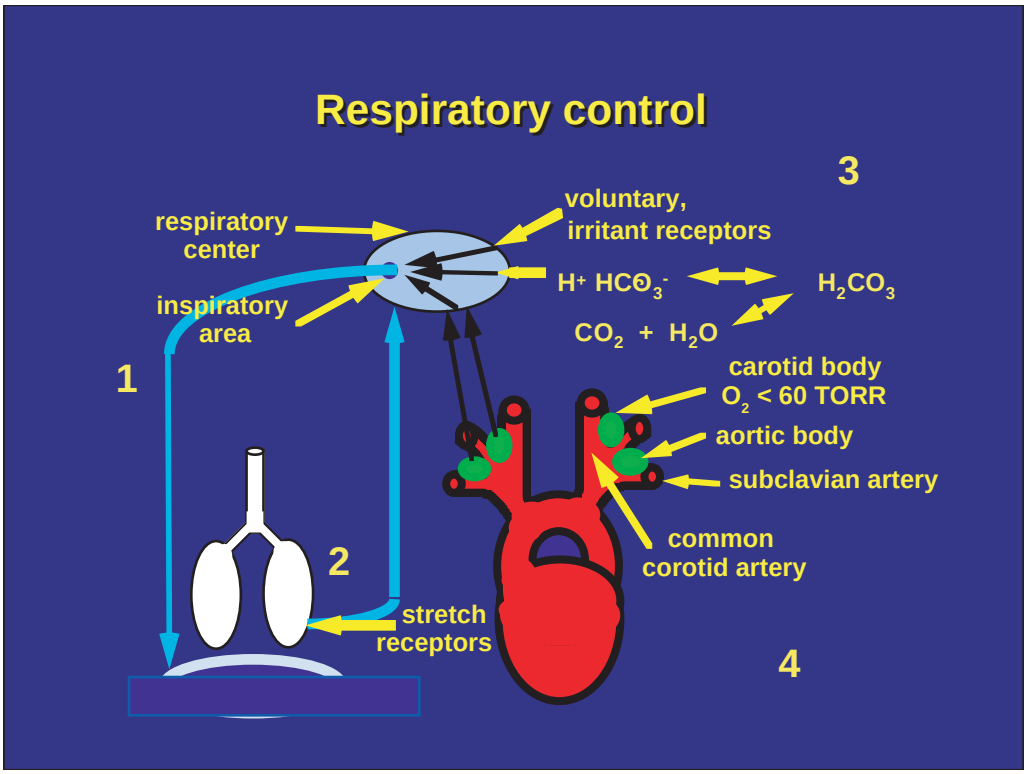

Figure 8-6. Stimulus to the inspiratory area of the respiratory center stimulates the diaphram to contract. This increases the volume of the chest cavity, drawing air into the lungs as they expand. Stretch receptors send an inhibitory signal to the respiratory center. The diaphragm relaxes, and the elastic fibers of the lungs cause them to collapse, forcing the air out. The mechanism can be stimulated by high hydrogen ion concentrations, low pH, high CO_2 concentrations, or low O_2 levels.

patient to ensure that adequate arterial oxygen levels are maintained and that CO_2 levels do not increase. Hypoventilation is characterized by a reduction in arterial oxygen tension and an elevation of CO_2 tension. With the advent of pulse oximetry, it is now possible to easily monitor oxygen saturation of hemoglobin.

Pulse oximetry shows the oxygen saturation of hemoglobin. In addition, most machines also display pulse rate. Knowing the saturation of hemoglobin, one can approximate the arterial oxygen tension, assuming a normal pH of the blood. Although 90 percent saturation provides reasonable assurance of adequate arterial oxygen tension, 95 percent is preferred. Although oximetry is not equivalent to capnography, it is valuable in alerting the dentist that ventilation is depressed.[54]

The importance of monitoring a patient's respiration cannot be overemphasized. If a patient is awake and responding to verbal commands, we can assume the patient is safe. If the patient is unconscious (asleep?), we must have more concern. Several studies of medical and dental anesthesia have shown inadequate ventilation to be the most common cause of death or brain damage. As practitioners, we must be prepared to monitor and assist respiration should it become necessary.

The Reservoir Bag

In the 1960s, watching the reservoir bag was used on several popular television programs as a means of determining when it was time to discontinue surgery and give condolences to the next of kin. We have now all been taught via television to read electrocardiographs (ECGs) and to recognize flat line. Some feel the movement of the bag can be used to monitor respiration. There have been several studies that show one should not depend on movement of the bag as an accurate indication of the adequacy of respiratory exchange. It will indicate respiratory rate.

Pulse Oximeter

The advent of an affordable pulse oximeter has made our lives much easier and patients' lives more secure. By passing two different frequencies of light through various tissues, reading the absorption of the two frequencies, and evaluating these differences, a pulse oximeter can determine the percentage of oxygen saturation of the arterial blood with great accuracy. In addition to O_2 saturation, most equipment also shows pulse rate, and some shows a pletysmograph of the pulse wave. The use of such monitoring has made general anesthesia much safer and, consequently, has decreased the frequency of tragic outcomes.

However, there is at least one possible caveat to their use: If a patient is given supplemental oxygen, his or her hemoglobin saturation will approach 100 percent. In patients with severe respiratory complications, oxygen saturation could be normal even though exchange rates were inadequate to cleanse the blood of CO_2. This could lead to high CO_2 levels and result in low pH of the blood. This potential problem can be circumvented by limiting sedation to patients with no significant respiratory problems.

Capnography

Capnography is very sensitive to respiratory depression or apnea. This equipment measures the CO_2 of a patient's expired gas. It then gives a reading of the concentration of CO_2 in these gases. This information can be invaluable when monitoring patients with respiratory problems or those undergoing general anesthesia, but it is not necessary for the sedated patient.

Benzodiazepines

It was established that barbiturates, meprobamate, and alcohol all affect the chlorine channel in brain neurons. They hyperpolarize the neuron, increasing its threshold for depolarization. Benzodiazepines act at a different but closely related site. Alcohol, barbiturates, and meprobamate all act at the same site, and all put animals to sleep with only modestly higher doses than are required for sedation.

It was shown that all these drugs interact with the neurotransmitter gamma amino butyric acid (GABA). When GABA binds with a receptor site on the neurons, it slows the neuron's rate of firing. It serves to modulate the nervous system.

Specific benzodiazepine receptors exist in the brain. If either GABA or a benzodiazepine is present, the other's binding ability is enhanced. Thus, the effects of the benzodiazepines are explained by the increased activity of GABA.[55 56]

The receptor sites are concentrated in parts of the brain that regulate emotional behavior. The advantage to benzodiazepines is their ability to relieve anxiety. They produce some drowsiness and, unfortunately, are somewhat addicting. Tolerance develops with continued use, and withdrawal occurs when the drug is stopped. However, the extent of tolerance and withdrawal are less than what is seen with barbiturates.

Historically, we have used barbiturates

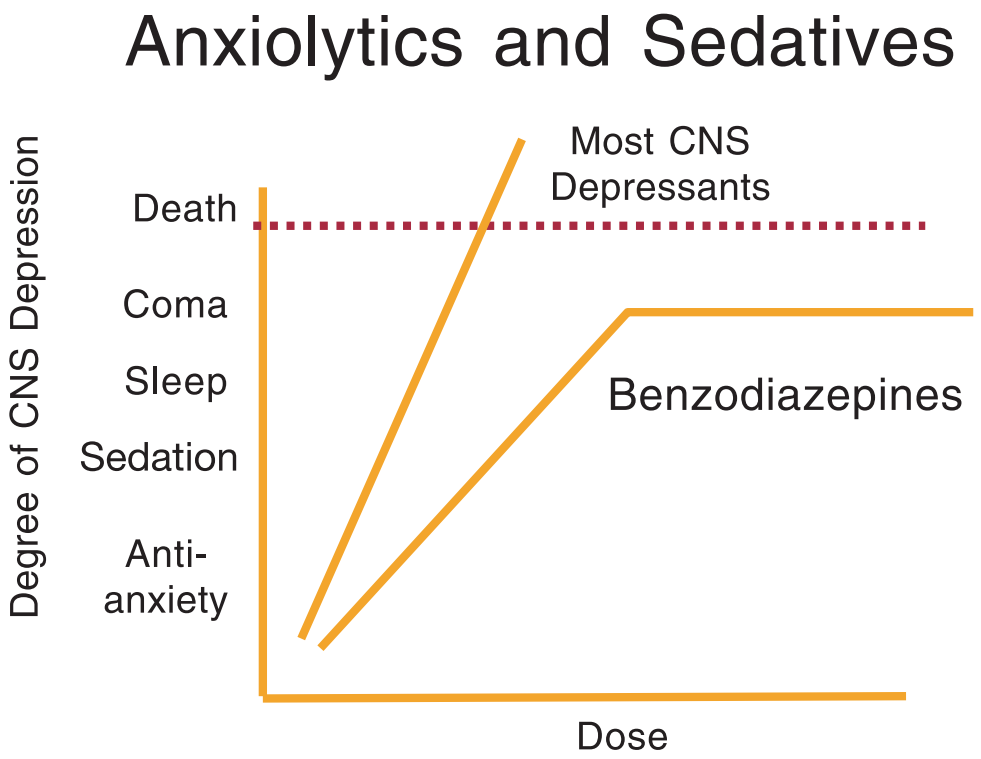

Figure 8-7. Most central nervous system (CNS) drugs if given in large enough quantities will result in death, usually from respiratory depression. When given as a single agent, benzodiazepines can be given in very large doses without causing death. They have a wide margin of safety.

and narcotics, both of which have significant effects on respiration and circulation. The most clear-cut advantage of the single-agent, benzodiazepine sedation is the fact that overdoses are rarely lethal. In the case of barbiturates, the lethal dose is only a few times greater than the dose necessary to cause sleep (see Figure 8.7).

To deactivate most oral sedatives, we must wait for the drug to be excreted or metabolized. In the case of diazepam it is metabolized in liver to another sedative, oxazepam (Serax), which is available as a long-term sedative on its own. Triazolam, along with midazolam (Versed), have the shortest half-life of the benzodiazepine drugs; both are in the one- to two-hour range. Midazolam is normally considered to be an intravenous drug, although it is being used orally and as a nasal spray. It is available in Europe as a tablet. Unfortunately, it has been shown to have a noticeable respiratory depressant effect in higher doses.

The Advantages of Oral Triazolam Sedation

Oral sedation with triazolam is simple to administer, and because of the nature of the drug, it is convenient and safe to use. Triazolam is readily available from any pharmacy. Reports of adverse drug reactions are rare and tend to be relatively mild. A major plus for all oral sedatives is that it is not necessary to administer an injection or start an intravenous line. (The last thing most phobic patients need is a needle puncture before they are sedated.) Getting an IV started in a phobic patient can be the most difficult part of a dental appointment. Patients readily accept oral sedation.

Triazolam is a drug that has been around

for some time but has been used primarily as a sleep aid. In this context, it has received bad press because of side effects that have shown up in patients who used it over an extended period of time. In the early 1990s, it is the most commonly prescribed sleeping pill used in the United States; 7.2 million prescriptions were written annually.[57] It should be emphasized that triazolam is not approved by the FDA as a sedative for dental purposes.[58–60] This is an "off-label" use.

Triazolam comes close to being an ideal drug for dental sedation.[61] It has the advantage of being absorbed rapidly, achieving peak blood levels in 1.3 hours. Its half-life is two to three hours. In addition, it may be up to eight times more effective as a hypnotic than diazepam. Yet, triazolam has very little effect on the circulatory or respiratory systems. Several studies have shown no changes in blood pressure, pulse, or percentage of oxygen saturation, and only a slight change in respiratory rate. The high incidence of anterograde amnesia on conscious patients further endears it to the dental practitioner. Patients do not have to be asleep for their dental treatments if they can be relaxed enough for us to do the required procedures and not have any memory of the procedure.[62–65]

Triazolam's relative lack of respiratory and cardiovascular sedation is important for safety. Safety is dependant on the ratio of the L/D 50 dose (that dose usually fatal to 50 percent of study animals) to the E/D 50 dose (concentration that provides sedation to 50 percent of study animals).

It would be ideal if this ratio were constant for humans. If this ratio held for humans, it would take a tablet about the size of a bowling ball to have fatal consequences. Unfortunately, this is not true. The greater the difference between the E/D 50 and L/D 50, the safer the drug. Several patients have committed suicide with triazolam. From postmortem blood samples, it was estimated that one person ingested 26 0.25-mg tablets. Another individual was found dead in a hot tub. It was estimated she had taken 10 tablets. So it is possible to overdose and die, but the amounts necessary are well beyond what is necessary for dental sedation.[66]

Ambien (zolpidem) has been used by some dentists to replace triazolam. Ambien is an agonist of the GABA-benzodiazepine omega-1 receptor site. It has a similar half-life to triazolam, but is a nonbenzodiazepine hypnotic of the imidazopyridine class. Some claim it has a little faster absorption than triazolam; however, the manufacturer reports maximum blood levels occurred at 59 and 121 minutes for 5- and 10-mg doses. It has a half-life of 1.4–4.5 hours

Yagiela suggested lorazepam (Ativan) would be an alternative to multiple doses of triazolam.[67] Lorazepam has a 10–20-hour half-life and a slower uptake. He suggested it should be taken two hours prior to starting treatment. Five hours later, less than half of the drug has been deactivated. Ten to 20 hours later half the effect is still present. Be concerned about the patient driving the day after treatment. It makes more sense to use a drug with a shorter half-life and give a supplemental dose after one to two half-lives have passed. In this way, recovery should be faster. Lorazepam makes sense if you will give only one dose of a sedative drug, and you need sedation for four or more hours.

Pharmacology of Triazolam

The unique properties of triazolam are attributed to its chemical configuration. The nitrogen atom prevents it from being water-soluble. Midazolam has a carbon in this position and, thus, is water soluble and suitable for IV administration.

One chlorine atom is responsible for potency. Without this chlorine, the drug is one-fifth as potent. Larger alkyl substitutions also decrease potency. The second chlorine is necessary for benzodiazepine action. Bromo

and nitro substitution are only weakly anxiolytic. The nitro version is also anticonvulsant, as illustrated by clonazepam. The triazolo ring and attached methyl group are responsible for the rapid oxidation by the liver enzymes, resulting in a short elimination half-life and conversion to metabolites that are rapidly excreted. The methyl group also makes a drug more potent.[68, 69]

Absorption

Triazolam reaches a rapid peak within 1.3 hours.[70] It works faster in the elderly and in young women.[71] It also works more rapidly in daytime than at night, due to a longer predose fasting period. It is as much as two times quicker after a 12-hour fast.[72] One study reported that 85 percent of the drug is absorbed into the bloodstream. The study also found that it is absorbed 28 percent more quickly if given sublingually, where some of it is absorbed but most of it is swallowed.[73]

Distribution

The distribution of triazolam shows no difference in obese and normal patients. It is 89 percent bound to plasma and 49 percent bound to serum proteins and crosses readily into the central nervous system because of high lipid solubility. It also crosses the placental barrier and has been found in milk of rats.

Metabolism and Elimination

Triazolam is oxidized in the first pass through the liver and the lining of the gut by the cytochrome P450-mono-oxygenase system. The P450 system is made up of many enzymes. Triazolam is metabolized by the 3A4 enzyme. Tagamet, cimetidine, erythromycin, isoniazid, possibly some oral contraceptives, some anti-HIV drugs, delavirdine (DLV), efavirenz (EFV), and grapefruit depress the cytochrome P450-mediated oxidatative system, thus reducing the first-pass liver clearance by decreased metabolism and reduction in hepatic blood flow.[74] The absence of an enzyme in some people can be idiosyncratic or associated with certain patient subsets. Southeast Asians may have less 3A4 enzyme (see Figure 8.8).

Triazolam has no active metabolites. As mentioned, its half-life is approximately two to three hours but is slower at night. The half-life is longer in the elderly because of lower liver oxidizing capacity. There is no change with kidney dialysis, but the half-life is slower with cirrhosis. Ninety-one percent is eliminated in urine and 9 percent in feces within 72 hours.[75 76]

Central Nervous System Effect

All the benzodiazepines have clinically useful antianxiety, sedative-hypnotic, anticonvulsant, and skeletal muscle relaxant properties. They all depress the CNS to some degree, tending to be more antianxiety oriented as compared with barbiturates and other sedative-hypnotics. They depress the limbic system and areas of the brain associated with emotion and behavior, particularly the hippocampus and the amygdaloid nucleus. The major effects are attributed to an interaction with the GABA receptor complex.

Cardiovascular System Effect

In normal therapeutic doses, the benzodiazepines cause few alterations in cardiac output or blood pressure when administered intravenously to healthy persons. Slightly greater than normal doses cause slight decreases in blood pressure, cardiac output, and stroke volume in normal subjects and patients with cardiac disease, but these changes are not usually clinically significant. Triazolam did not affect cardiovascular dynamics in doses four to eight times greater than normal.[77]

Bioavailability

- Fraction of unchanged drug reaching the systemic circulation after administration by any route.

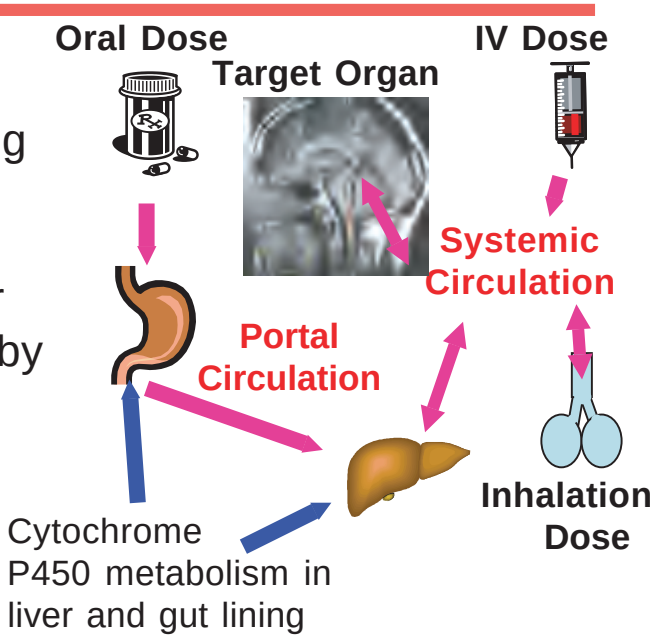

Figure 8-8. Benzodiazepine drugs are absorbed through the intestinal wall, where metabolic breakdown is initiated by the cytochrome P450 metabolic enzymes. They travel to the liver via the portal circulation. When in the liver, further metabolism occurs prior to entering the systemic circulation. When in the systemic circulation the drugs can affect the target organ, the brain.

Respiratory System Effect

Most benzodiazepines are mild respiratory depressants. Given alone to a healthy patient they have little effect; however, they can potentate other CNS depressants. Midazolam is one that can cause respiratory depression and apnea. Triazolam did not depress respiratory response to CO_2 in doses four to eight times normal.

Reproduction

In rats, slightly reduced fertility occurred, but the drug did not affect their postnatal development.

Recovery

One method of measuring recovery, a visual coordination study (following a randomly moving dot with their finger), had patients back to normal in five hours after ingesting 0.25mg and in 11.5 hours after ingesting 0.5mg benzodiazepins. Reported side effects include 8 percent sleepiness; 4 percent headache; and dizziness, neuritis, and dry mouth.

Triazolam Pharmacology

Before practitioners use any medication, they should be knowledgeable of its pharmacology. Likewise, every practitioner, but particularly those using sedatives, should be able to initiate resuscitation (including cardiopulmonary resuscitation) and ventilation. The equipment necessary to provide these emergency treatments must, of course, be available.

There are a few absolute contraindications to the use of triazolam. Patients who are known to be hypersensitive to triazolam or

other benzodiazepine drugs should avoid its use. Myasthenia gravis patients should not be treated, as triazolam has a muscle relaxation effect. Glaucoma patients should avoid all benzodiazepines, as these drugs raise intraocular pressure by increasing the outflow resistance to aqueous humor.[78] (This can often be reversed by pilocarpine.) All the benzodiazepine drugs are teratogenic and should not be given to pregnant women. As triazolam has been shown to pass through the mammary glands of mice into the milk, it should not be given to lactating mothers. As it is a CNS depressant, it should be given cautiously to anyone on other CNS depressants or drugs that suppress the P450 metabolic system.[79]

Relative Contraindications

There are no detailed studies of triazolam's use as a sedative with pediatric and geriatric populations, and practitioners should be cautious when giving triazolam to these groups. Some clinicians teach not to use it with patients under 18 or over 65 years of age. There have been reports of suicide attempts by psychiatric patients. Suicidal tendencies were unmasked, creating this paradoxical behavior.[80] Several European countries have outlawed triazolam. One report showed an incidence of psychotic episodes after triazolam. However, the study was done in a psychiatric hospital, where many patients have psychotic tendencies. The final relative contraindication is the fact that triazolam has not been approved by the FDA for dental sedation or the sedation of children.

Adverse Effects

Adverse effects have been reported in less than 4 percent of patients. Most adverse effects were with doses greater than 0.5mg or when combined with other CNS depressants. As with all sedatives, patients cannot drive, operate machinery, or undertake any activity that could be hazardous. This includes such activities as walking unaided, climbing stairs, and so on. They should not undertake positions of responsibility or care of children and should not make important decisions (legal, monetary, and so on) for the rest of the day. They should not have alcohol or other sedatives for 24 hours.[81]

The office should have an effective, efficient emergency protocol. This should include a person to be continuously in the room with the patient from the time of administration of the drug until the patient is judged able to leave the office. The patient should not be allowed to sleep at any time. Oxygen saturation should be continuously monitored and recorded starting before administration of the drug. Vital signs should be taken at regular intervals such as every 15 minutes or even more often if there is any indication of over-sedation.

Management of adverse reactions should be planned before the drug is used and should be reviewed on a periodic basis. It should be noted that most adverse effects would be prevented by complete history taking, physical examination, and appropriate adjustment of drug dosage. Recognition of an emergency situation must be followed by initiation of a stabilization routine. This essentially entails the A-airway, B-breathing, and C-circulation of basic cardiac life support. Opening and maintaining a patient's airway is of paramount importance, as is monitoring vital signs. Calling the Emergency Medical Service by dialing 911 should follow if any doubt exists as to how to proceed.

Use in the General Dental Office

Over 15 years, this author has used triazolam more than 400 times. The patients come to the office one hour before we want to start their dental procedure. They are monitored by recording blood pressure, pulse rate, and pulse oximetry. The drug dose is determined by the patient's weight and purposely kept

conservative—less than might be necessary. We usually administer a supplemental dose sublingually if at the 30-minute mark we see no signs of sedation.

My patient population has ranged from 7 to 83 years of age and from 60 to 320 lbs.[103] All patients were ASA 1 or 2 with no history of recent illness. All adult patients were dental phobics who requested IV sedation or general anesthesia for their procedures. The children had previous attempts at treatment with conventional methods, including nitrous oxide, which were unsuccessful.

Cardiovascular and respiratory parameters measured and recorded included blood pressure (systolic and diastolic), heart rate, and oxygen saturation. With uncooperative children, only heart rate and oxygen saturation could be measured. Cardiovascular parameters were recorded every 15 minutes. During the procedure, oxygen saturation was continuously monitored with a pulse oximeter.

After recording initial baseline data, oral triazolam was dispensed. Many authors have reported on the appropriate dosage for sleep enhancement. Suggested dosages range from 0.125mg to 0.5mg.[82, 83, 84, 85, 86, 87]

After a discussion and completion of an informed consent document and recording of preoperative vital signs, a dose of triazolam is administered. An assistant stays in the operatory with the patient for the next hour, taking vital signs, blood pressure, pulse, and respiration every 15 minutes with instructions to alert me if there is any change. The assistant is instructed to talk with the patient to ensure that they remain awake. I check to see whether there is any sign of sedation at 30 minutes. If there is no sedation evident, we will administer one-half the original dose. If even slight sedation is noted at that time, we normally will have adequate sedation for the procedure. (Many patients will be disappointed at the end of the 40 minutes by the relative lack of sedation. They are assured that this is normal, and they will be adequately sedated by the time we start.)

As mentioned, we decide to administer one-half the initial dose after 30 minutes if there is no evidence of sedation. Supplemental dosages were necessary for about 10 percent of patients. We used the following protocol to determine the dosages. Dose in mg = 0.25 mg + 0.125 mg for every 70-pound weight increment over 40 pounds.[88]

Patients reported a decrease in apprehension that was greatest the first 30 minutes, with the second largest drop between 30 and 60 minutes. About 50 percent had moderate to complete forgetfulness of the appointment, and most did not remember the ride home. There were no significant changes in blood pressure, pulse rate, or oxygen saturation.

It should be emphasized that no patients slept, snoozed, snored, or napped. All were awake and responded to verbal commands without painful stimulation. We have had no adverse effects on any of my patients. We did have three who were not sedated adequately to treat.

Protocol in Our Office

It should be stressed, and I will repeat again, that we do not want a patient who is asleep. If a patient sleeps, they are oversedated and should be kept awake by verbal commands, or if this does not work, the drug should be reversed. We do not worry whether the patient is disappointed by their level of sedation because the amnesia that is common to this technique will allow them to forget most, if not all, of the appointment. It should be emphasized with children that they might still cry during the appointment. If they are controlled enough to allow dentistry to be safely done, they are adequately relaxed. Crying, although distracting to the practitioner, is an indication of adequate ventilation. I would suggest not using any form of sedation on children under 7 years of age, unless you are trained in pediatric

anesthesiology and are equipped and trained to handle general anesthesia and all the complications of anesthesia.

The Procedure

At a pre-appointment interview, the medical history is reviewed to determine that there are no contraindications to triazolam, the procedures, or from possible risks. Benefits and options are discussed with the patient or, in the case of children, with their parents.

Patient Selection

1. The patient is over 7 years of age and 70 lbs of weight.
2. The patient is ASA 1 or 2. I suggest not treating any person who has any medical problem, however slight.
3. Have a signed consent form.
4. Start with a dose of triazolam appropriate for the patient's size.
   a. 70 to 110 lbs gets 0.25 mg
   b. 110 to 180 lbs gets 0.375 mg
   c. 180 to 240 lbs get 0.5 mg
   d. 240 plus get 0.625 mg (see Figures 8.9 and 8.10)
5. If after 30 minutes you see absolutely no effect and if the patient tells you they do not feel any different, give half the original dose sublingually. If they show even a very slight effect, no second dose is necessary (see Figure 8.11).
6. Two hours later you can give half the total dose if you have another hour to go and the patient is much less sedated than they were at 60 minutes. You are giving a dose equal to the amount that has been metabolized.
7. If you need a little more sedation toward the end of a case, augment with nitrous oxide.
8. Only use one oral drug, triazolam. Have the reversal agent and be prepared to inject it into the floor of the mouth if the patient does not respond to verbal command without any tactical stimulation. A pinch will arouse the patient until you can inject the reversal agent. Reverse the sedation as they are starting to get deeper, not after they are under general anesthesia.
9. We are not talking SLEEP, DOZE, SNORE, or NAP. We are talking awake with anxiolysis.

Dose (mg) = 0.25mg + 0.125mg (for every 70lb weight increase > 40lbs)

Therefore mean dose = 0.005mg/lb or 0.5mg for 180-pound man

- Triazolam (Halcion) oral sedation can be used effectively over traditional intravenous or inhalation sedation.
  - 70 lb to 110 lb = 0.25 mg
  - 110 lb to 180 lb = 0.375 mg
  - 180 lb to 250 lb = 0.5 mg
  - 250 lb and greater 0.625 mg
- Dosing is simple (based on the "Q-factor").
  - Give half the original dose if no effect at 30min.
  - Give half the original dose every 2 hr. if sedation lightens.
- Good body of evidence reporting its successful use.

Figure 8-9. Dosage calculation: Dose in mg = 0.25mg + 0.125mg for every 70 lb weight increase over 40 lbs. This equals 0.5 mg for a 180-pound man. If no sedation is observed at 30 minutes, a second dose is administered that is half the original dose. For long cases additional doses may be necessary as the drug is metabolized.

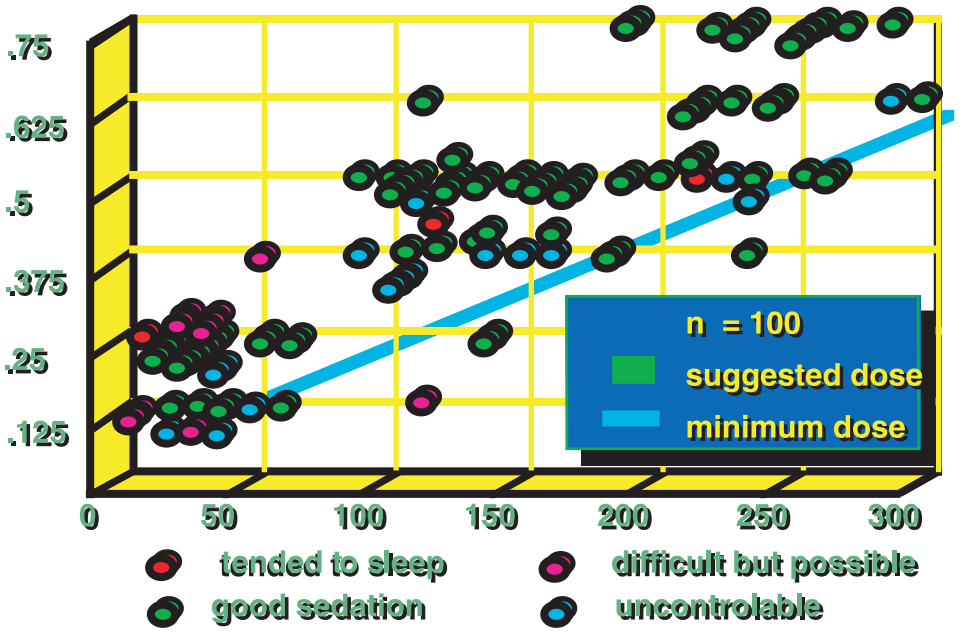

Figure 8-10. Weight vs. dose of triazolam. This was an early graph of our use of triazolam in 110 patients. It was from these data that I developed a dosing scheme relating to the patient's weight.

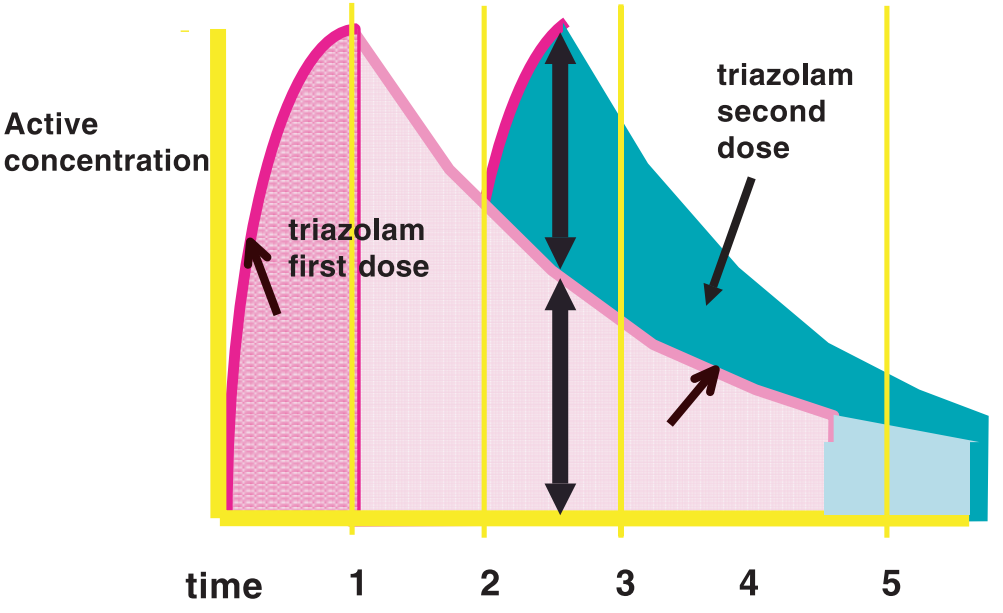

Figure 8-11. Titration of triazolam: Long cases may require a second dose that equals the amount of drug that has been metabolized. Based on information from the following two references: (1) Friedman, H. et al. 1886. Population study of triazolam pharmacokinetics. *Br J Clin Pharm.* 22(6):639–42. (2) Derry, C.L. et al. 1995. Pharmacokinetics and pharmacodynamics of triazolam after two intermittent doses in obese and normal-weight men. *J Clin Psychopharmacol.* 15(3):197–205.

10. Never leave the patient alone in the room.
11. Never leave a male dentist, hygienist, or assistant alone with a female patient.
12. Monitor BP, pulse, and oxygen saturation continuously after you give the initial dose.
13. If the patient needs to use the restroom, they must be accompanied by a same-sex staff person.
14. The patient must be with a responsible adult the rest of the day.
    a. They are to have no alcohol or other sedatives for 24 hours before the appointment.
    b. There should be no chance that they are pregnant.
    c. They should have none of the other contraindications.
    d. They cannot drive, operate machinery, or undertake any activity that could be hazardous. This includes such things as walking unaided, climbing stairs, and so on.
    e. They should not undertake positions of responsibility, such as care of children, and should not make important decisions—legal, monetary, and so on, for the rest of the day.[89, 90, 91]

It is stressed that we are not attempting nor is it our intent to have the patient sleep, although they might experience amnesia for some or all of the appointment. I have found that about 75 percent of patients have amnesia from the time we start the procedure (60 minutes after administering triazolam). The amnesia lasts for 2–3 hours. All patients have had some amnesia or forgetfulness of the appointment.

When the appointment is complete, we keep the patient in the dental chair until they are able to walk out with someone holding their arm. The dentist is the one to determine whether they are able to safely leave the office**.** You are looking for a noticeable decrease in sedation. Postoperative instructions, the same as were given to the patient in the pre-appointment, are reviewed with the adult who is going to take the patient home and watch over them the rest of the day. I assess and record the patient's level of sedation prior to his or her leaving the office. In addition, my home phone is given to this accompanying adult, who is encouraged to call if they have any questions or problems. Finally, an assistant accompanies the patient out to the car, supporting the patient so there is no chance of a fall. The patient is seated in the passenger seat, and the seat belt is buckled.

It should be noted that a second appointment will normally be easier than the first. It has never been necessary to use a higher dose at the second appointment if the dose on the first appointment was adequate. Also, as this is a class IV drug, it is necessary to keep careful accounting records of its use.

Status of Triazolam

UPJOHN

The Upjohn company distributes triazolam in the United States. They make no claims of its usefulness as a dental sedative, nor has it been tested for use with children. The Upjohn company made it very clear to me in a letter that the use of this drug for dental sedation and with children is investigational in nature and not supported or encouraged by the company. The patent has run out for triazolam. Consequently, there is little chance that it will ever be certified for dental sedation.

FDA

The FDA does not recognize triazolam's use for either dental or pediatric sedation. A practitioner must recognize that should there be a problem, the lack of FDA approval would create problems from a medical-legal standpoint. Lack of FDA approval does not,

however, prevent our using the drug for sedation.

Recordkeeping Requirements

The Drug Enforcement Administration, a division of the U.S. Department of Justice, has a booklet that is available from any DEA office, entitled, *Physician's Manual, An Informational Outline of the Controlled Substances Act of 1970.* This manual spells out the requirements of recordkeeping, storage, inventory, security, and so on required for prescribing and dispensing a controlled substance. Triazolam is a schedule IV substance.

To administer, prescribe, or dispense any controlled substance, a physician (dentist) must be registered with the DEA. The DEA requires that "The registration must be renewed every three years and the certificate of registration must be maintained at the registered location."

"It is necessary for dentists to keep records of drugs purchased, distributed and dispensed. Having this closed system, a controlled substance can be traced from the time it is manufactured, to the time it is dispensed to the ultimate user."

"All controlled substance records must be filed in a readily retrievable location from all other business documents, retained for two years, and made available for inspection by the DEA. Controlled substance records maintained as part of the patient file will require that this file be made available for inspection by the DEA."

"A physician (dentist) who dispenses controlled substances is required to keep a record of each transaction."

Inventory requirements

"A physician (dentist) who dispenses or regularly engages in administering controlled substances is required to keep records and must take an inventory every two years of all stocks of the substances on hand."

Security

"A physician (dentist) must keep these drugs in a securely locked, substantially constructed cabinet or safe."

In my office, the triazolam is kept locked in a keyed locker, which is permanently attached to an office wall. Inventory sheets are kept in a book with patient record forms. This sheet shows date and patient name, age, and weight and has space for comments. The inventory total is changed with each drug administration so as to provide a running total of the drug inventory. When restocking the drug supply, a copy of the prescription is attached to the inventory sheet.

Patient Records

Patient records are kept for all treatments. These records would be the same for any sedative agent except when nitrous oxide is used with no other sedative drugs. These records include the consent form, postsedation evaluation, and a sedation record that includes blood pressure records, pulse rates, and pulse oximeter readings. These values are taken and recorded preoperatively and at 15-minute increments from the drug administration until the case is completed. The patient's medical status (ASA rating) is recorded along with age, sex, weight, amounts of drug administered, name, date, and whether this is the first administration of this sedative.

Sedation records are necessary for several reasons. First, they establish a baseline and would be one of the first indicators of a potential problem. If any of the measured parameters start to change, we should immediately be alerted and start corrective action. Second, the stress of an emergency makes time sequencing difficult for the practitioner. It becomes all but impossible to recall vital signs and the times they were recorded. Complete records can provide clues about the case and possible solutions

to our problem as it progresses. (At what point did we lose verbal contact? How long has the patient been at this level? Did the change come on rapidly or have vital signs been slowly changing for some time?) Lastly, in the event of legal action, complete and accurate records are a must for one's defense.

Flumazenil (Romazicon) Reversal Agent

It would be a great advantage to have a medication that would reverse the effects of any drug we use. This is particularly true of any drug that requires excretion or metabolism to be deactivated. When using drugs intravenously, small test doses can be given and augmented as necessary to achieve the desired effect. These test doses go directly to the CNS and show their effect. They are then redistributed to the rest of the tissues of the body, effectively diluting the effect in the case of an overdose or sensitivity to an agent. Titration with oral drugs is very slow. It takes considerable time before it is obvious that we have a problem. Redistribution and saturation into the body have already taken place and are of little aid. In the case of overdose, there is little we can do except treat the symptoms of the overdose and support respiration and circulation. For this reason, a reversal agent for oral drugs is very desirable. The reversal agent for benzodiazepines is flumazenil.

History

In 1974, Haefely hypothesized and showed that benzodiazepines act by increasing the effectiveness of the most important inhibitory neurotransmitter, GABA. Later, several compounds were produced that had a greater affinity for this site than diazepam. One of these, flumazenil, was selected as an antagonist for clinical trials.[92]

Pharmacology

Flumazenil was shown to prevent benzodiazepine sedation if given before the benzodiazepine and to reverse the effect if given during or after the sedative drug. To reverse sedation or general anesthesia of benzodiazepine drugs, flumazenil is administered intravenously in titrated doses from 0.2-to-1.0 mg doses. In the case of overdose, 2.0 to 3.0 mg may be necessary.[93]

Toxicity and Safety

"Flumazenil has a high therapeutic index and a wide margin of safety." It showed minimal effect on patients with ischemic heart disease. No withdrawal symptoms were seen when it was given to patients who had been on diazepam or triazolam for up to 14 days. Some symptoms were seen in patients who had been on lorazepam. It should not be given to patients with severe head injuries and unstable intracranial pressures.[94] When given to patients with panic disorder, 2mg of flumazenil intravenously precipitated panic attacks. It had no effect on healthy patients.[95]

Use with Children

Jones administered flumazenil to 40 healthy children aged 3–12 years of age after they had received midazolam for the induction of anesthesia. The drug was given along with a placebo, and the efficacy of antagonism was assessed. Those receiving the active drug awoke approximately four times faster. There were no cases of resedation and minimal changes in the cardio-respiratory variables.[96]

Use with Adults

The half-life of flumazenil at 54 minutes (.7 to 1.3 hr) is less than triazolam, midazolam, and diazepam, so you may see some rebound of effect (see "Resedation" section

later in this chapter). Sedation was gone within 2 to 5 minutes. I have seen the reversal drug used sublingually in the floor of the mouth. The pain of this injection noticeably aroused the patient. Their sedation was obviously lessened within two minutes; however, maximum reversal took 10 minutes for IV administration and 20 minutes for sublingual. In both cases, most of the effect occurred in the first five minutes.

Contraindications

Flumazenil is contraindicated in patients with a known hypersensitivity to flumazenil or to benzodiazepines, in patients who have been given a benzodiazepine for control of a potentially life-threatening condition (for example, control of intracranial pressure or status epilepticus), and in patients who are showing signs of serious cyclic antidepressant overdose.[97]

Resedation

Because of the relatively short half-life of flumazenil, 54 minutes, it is possible that its reversal effect could disappear before the sedative effect of triazolam, with its half-life of one to two hours (see Figure 8.12). Midazolam has a similar half-life (one to two hours), and several studies have failed to show significant resedation if appropriate doses of midazolam had been used.[98–100] Resedation has been shown with diazepam,[101] which has a much longer half-life (20–50 hours), and with larger doses of midazolam.[102] Until studies have been reported showing no resedation with triazolam, a patient who requires flumazenil should be ob-

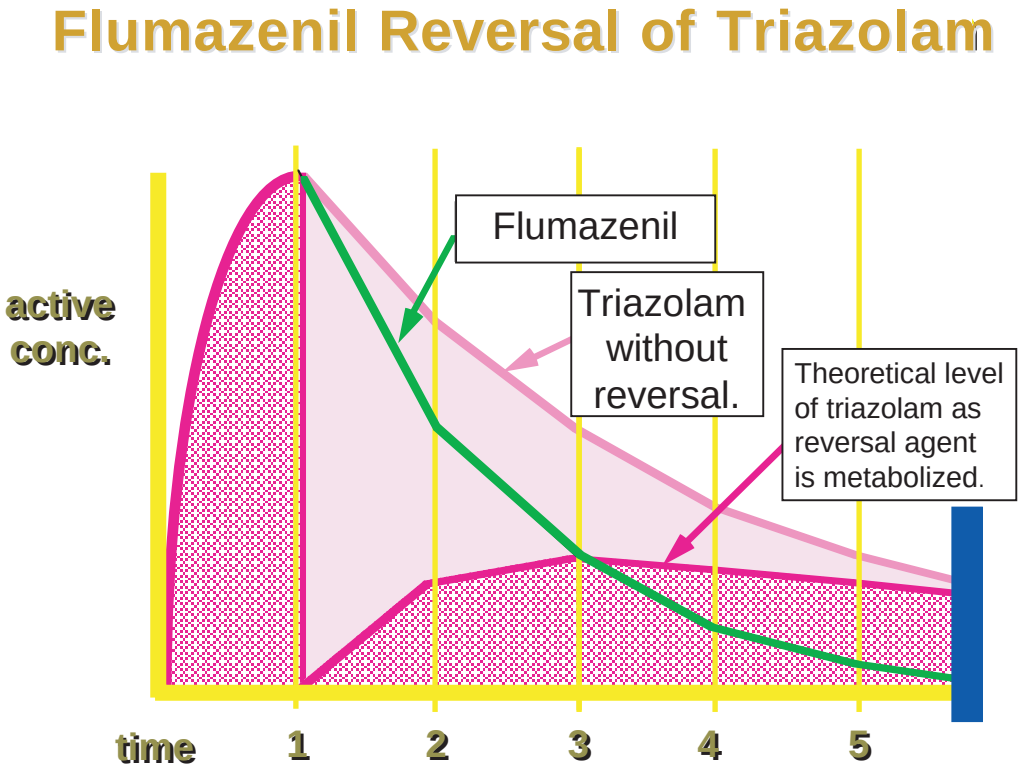

Figure 8-12. The figure shows the reversal with Flumazenil. At time 1 the triazolam is completely reversed. At time 2 one hour later, half the Flumazenil has been metabolized, and part of the effect of the triazolam has rebounded. This effect increases through hour 3.

served for several hours after reversal to be positive resedation does not occur. There is a risk that with reversal the patients may feel normal and attempt activities they are not capable of safely performing.

With the introduction of this reversal agent, we are able to use triazolam with the comfort of knowing that we can reverse its sedation should we achieve an overdose. Of course, this in no way should cause us to use excessive doses of triazolam, nor does it relieve us of the responsibility of monitoring a patient's physical status and responding accordingly in the case of cardiovascular or respiratory depression.

Politics of Sedation

Oral conscious sedation has become a controversial subject for dentistry. The American Dental Association, specialty groups, and some state boards have attempted to severely limit the use of this very necessary and important technique.

In general, benzodiazepine drugs, and specifically triazolam, are very safe when used conservatively. Triazolam has become a drug of choice in dentistry because of its rapid uptake, short half-life, and amnesia. Oral sedation has come a long way toward addressing the unmet needs of phobic patients.

The ADA's guidelines state that titration or "giving a second dose of an oral sedative" is unpredictable and can lead to deeper levels of sedation. These guidelines limit the dose of an oral sedative to the maximum recommended dose (MRD). MRD is a FDA term. In the case of triazolam, it refers to the dose used as a sleep-aid for a patient who may be home alone and has nothing to do with dental sedation. The MRD for triazolam is 0.50 mg.

When you face a sedation/anesthesia emergency, you need all the skill and training you have acquired, previous experience handling such emergencies, and a little luck. This is an area where dental patients can and do die. Conservative dosing of triazolam for oral conscious sedation will never expose the practitioner to these moments of terror or the patient to theses risks. Always remember DO NO HARM! Death is forever.

Case Reports

It can be helpful to clinicians to have examples of situations in which a medication was actually used with a patient. Following are two care reports using triazolam in clinical settings.

Patient No. 1

A seven-year-old was sedated for dental treatment by a pediatric dentist. The patient left the office able to walk holding the hand of her mother. She went home and tended to sleep if left alone. The dentist's home phone line was out of order that evening. After trying to reach the dentist, her mother became concerned and called a local emergency room, who told her to watch the patient and that triazolam was not approved for use with children. The mother then called poison control and was again told that triazolam should not be used with children. The dentist relieved the mother's concerns when she reached him in the office the next day.

Patient No. 2

A 40-year-old black male about 6′1″ tall and 230 pounds had an uneventful sedation. At the close of the case, when he was judged to be ready to leave, his wife, a rather petite woman of 5′6″, was brought in and given postoperative instructions. At this time she mentioned they would be taking public transportation, a bus, home. Because I was concerned about her being able to help the patient on and off the bus, we kept him an extra hour to ensure that his wife would not have any problem getting him home. We did

not insist that the patient be transported by auto. The patient arrived home safely.

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