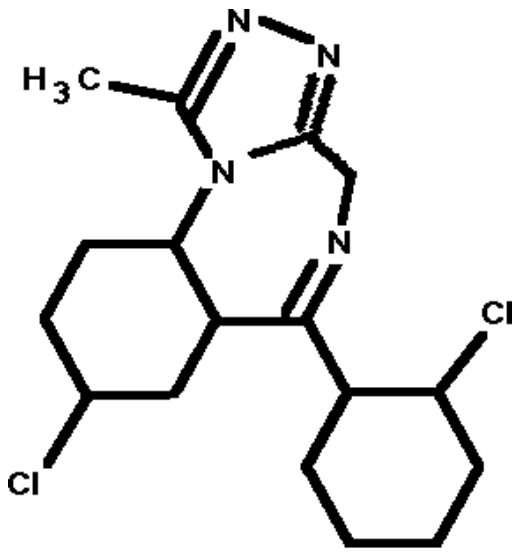

Triazolam

Sedation of Phobic Dental Patients with an Emphasis on the Use of Oral Triazolam, Halcion

by

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To my wife and best friend, Mariana,
who tolerated my many evenings
and weekends at the computer.

and

To my patients from whom I learn.

About the Author

Dr. Quarnstrom graduated from the University of Washington Dental School in 1964 and started his dental career as a dental officer in the United States Navy. He served with the Marine Corps and a Naval Construction Battalion the U.S., Okinawa and Vietnam. After the Navy experience, he spent a year at the Washington Hospital Center in Washington DC in the first year of a medical residency in anesthesia.

He has received fellowships in the Academy of General Dentistry, American Dental Society of Anesthesiology, and the International College of Dentistry. He has presented continuing education courses on nitrous oxide sedation, practice management, computer usage, electronic dental anesthesia, and I V and oral sedation. He has authored 20 papers and two manuals, produced a video tape and continues to do research in nitrous oxide sedation, electronic dental anesthesia, and Halcion oral sedation.

He has been in a private general practice in Seattle since 1967 and holds a the position of Clinical Assistant Professor in the Department of Dental Public Health Sciences at the University of Washington School of Dentistry and the Faculty of Dentistry at the University of British Columbia.

To the users of this manual:

When reading this manual, it is important to remember I am a practicing general dentist. As you read it will become obvious why I do not make my living writing. If you understand how I got into the study of dental sedation, it will help explain the approach I take.

I graduated from the University of Washington Dental School at the tender age of 23. I was not ready to start a dental practice so I joined the Navy. I assumed the worst that could happen to me was to be stationed on a ship and get to see some of the world, which at the time was at peace. One year later, I learned the importance of reading the fine print on contracts; as I made an amphibious assault across the beach at Chu Lai, Vietnam as the dental officer of a Naval Construction Battalion attached to the Marine Corps.

The foot peddle powered drill and other short comings of military dentistry left me wondering if I had made a mistake when I chose dentistry over medicine. To this end, I took the first year of an anesthesia residency when I got out of the Navy. One of the challenges I had faced as a military dentist was apprehensive patients. My thought was that phobic patients could be better treated with general anesthesia. In practice, I found IV sedation was adequate, much less complicated, safer and much less exciting than general anesthesia.

About the time I started practicing, nitrous oxide began a resurgence in popularity with general dentists. I made some unfortunate statements about dentists using anesthesia that were not prepared for the potential complications of general anesthesia. Fortunately, no one paid me much attention. Once I saw how nitrous was being use; I realized this technique was very safe. For the next 17 years I used IV sedation, and nitrous oxide to control apprehension in my practice and presented workshops on the use of nitrous oxide.

My practice developed a significant number of patients who depended on IV sedation for their dental treatments. Over the years, malpractice insurance premiums to provide this service continually increased. It finally came to the point where, economically, IV sedation was impractical. It was at this juncture that I started looking for an oral sedative to use with my more apprehensive patients. Halcion was suggested and as of this writing I have treated 150 patients with this drug. I have found little if any physiologic changes, have found patients receptive to this treatment and all the patients have been able to tolerate their dental procedures with the aid of this form of sedation.

The biggest problem in using Halcion has been its use as a sleep aid. Very shortly after starting to use Halcion in my office, it became the topic of many local and national TV, newspaper and magazine stories. The amnesia effect I find very beneficial for dental patients can be a problem for some patients when they use the drug daily to aid sleep. The elderly, in particular, can be come very disorientated because of the cumulative amnesia effect if Halcion is continued for an extended period of time.

It is my firm belief that it is best to use a few drugs you know well. Using a combination of drugs to treat a patient can greatly complicate patient management because the combination may have unwanted side effects. *Diazepam by it itself is quite safe, add alcohol and you can have devastating effects on respiration.* I have found Halcion to be nearly an ideal drug for dentistry due to its short half life, amnesia, few unwanted side effects and the existence of a selective reversal agent.

It is my hope that this manual will get other dentists interested in using sedative techniques. This manual should be considered a starting place. With a little study, a yearly course in CPR, conservative dosages and a pulse oximeter most dentists should safely be able to treat the apprehensive patient who cannot be treated with nitrous oxide.

I owe thanks to many people. My staff and patients have been helpful in putting up with my research endeavors. Ms. Samone Welch took my manuscript and made it look like I passed 10th grade English. Dr. Ted Jastak, Dr. David Donaldson, and Dr. Peter Milgrom encouraged and helped me with my research and teaching. My wife put up with having me at the computer evenings and weekends for the last several years as I worked on manuals and research. To all of these I say thank you very much.

F.C.Q.

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INTRODUCTION

"A USA Today article quoted ADA figures detailing that '12 million Americans are dental phobics. Another estimated 12 to 24 million suffer dental anxiety.' Coping with the difficult-to-manage patient has long plagued the profession. The high cost of malpractice insurance, government regulations that dictate who can and cannot be hospitalized, and the threat of litigation have caused many dentists to avoid under taking dental treatment on all but the most cooperative and easily managed patients and to turn their back on 36 million Americans who want but, for reasons beyond their control, are unable to undertake dental care in a usual manner."[1]

"A major problem that continues to have an impact on the teaching of anesthesia, pain, and anxiety control is the rising costs of liability insurance. In the 'real world,' annual premiums of almost $20,000 are required before the dentist can administer IV sedation."[2]

Whether or not we provide various forms of sedation depends on our education, state regulations, costs of insurance, our competency, and equipment. IV sedation is seldom used because of insurance costs, the need for postdoctoral education and, more recently, regulations in various states as to who can perform this technique.

Do you really want to see phobic patients?

When deciding on using sedation in our practice we must ask some important questions. First and foremost, we must honestly evaluate ourselves. Do we have the temperament to handle phobic patients? (At best, these patients are very difficult in many ways.) Can we handle the stress of the potential problems that can occur with sedation? Are we adequately trained to handle potential problems? (At a minimum, we and our staff should all have a CPR course on a yearly basis.) Do we have an emergency response team within a reasonable distance from the office to assist if an emergency should occur?

In this discussion, considerable space will be spent referring to the patient who is unconscious (asleep) and explaining why I am in no way comfortable with such a patient. On the other hand, the patient who is awake will respond to verbal directions and is, therefore, a safe patient. So long as your patient remains conscious, you can relax and enjoy performing dentistry. With proper preoperative evaluation, careful use of the right drug and calculation of its dose, you should never have a patient lose consciousness, that is, go to sleep. Should this occur, however, all else should cease until the patient is again verbally responsive. Some states have regulations that go one step further and require the equipment and training necessary to administer general anesthesia if a patient is rendered unconscious. But it is a little late to start buying equipment and getting training when you find, through misadventure or miscalculation, that a patient is no longer verbally arousable.

Once we discuss Triazolam, it will be-

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 - we'll all be able to breathe a sigh of relief. As you'll see later, flumazenil is reported to rapidly reverse the sedation of benzodiazepine drugs much as Naloxone does the opiate drugs.

Since there is a significant cost in lost productive time for training and purchase of equipment, both must be justified if one is going to start sedating patients. Because of the precipitous rise in malpractice insurance, several years ago many dentists who were qualified to administer deep sedation/general anesthesia had stopped offering this service. The phobic patient is left with the option of having teeth extracted at an oral surgery office under IV sedation or having restorative dentistry completed with oral sedation or nitrous oxide inhalation sedation. The purpose of this paper is to show that general dentists can provide these sedation services if they are interested, willing to take extra training and purchase some additional equipment, and will limit the drugs and the quantities of the drugs they use.

Who are the patients?

Adults: Phobic adult dental patients come in all sizes, shapes and colors and are phobic for many different reasons, both psychological and physical. Often these phobias developed when they were young children for all the usual reasons children develop dental phobias, including traumatic dental treatments. In some cases, troubles start much later due to an especially difficult treatment, particularly if pain control was incomplete.

It has also been postulated that a few people lack active pain suppression systems or suffer from depressed pain suppression mechanisms, including descending pain suppression pathways from the higher centers of the brain, and suppressed endorphin production or receptor systems. These patients have a very difficult time with pain control. They are the ones who appear to have a complete anesthetic block but who experience pain once a procedure is started and, in spite of the most diligent efforts of their practitioner, continue to have mild to moderate pain for most dental procedures.

My feeling in the past had been if they would only relax, we would have better pain control. I was blaming their lack of anesthesia on their apprehensions. I now wonder if I should have been blaming their apprehensions on the fact that most procedures they had undergone were done with only partial pain control because of their lack of endogenous pain suppression systems. This brings to mind the age old question of "Which came first, the chicken or the egg?" - a question that can thankfully remain unanswered so long as the practitioner treats the patient's apprehension symptomatically and adequately. Once patients are relaxed, adequate pain control is almost always possible.

Unfortunately, most adults never completely free themselves of their appre-

come obvious that the chance of problems hensions - but they will improve over time with careful treatment and good pain control. Many will be able to be treated with less potent forms of sedation, if they are seen regularly and have comfortable treatments. A few may even graduate to no sedation for their dental treatments. Other patients will be refractory to any attempt at treatment without profound sedation. We should accept all three types and be non-judgmental toward those who continue to need sedation to undergo dental treatment.

Children: Many children can be treated if sufficient time and effort is spent to communicate with them and if gentle, empathetic treatment techniques are used. However, the younger the child, the more difficult this task becomes. Below a certain age, most children will need some help if extensive treatment is required. Unfortunately, the younger child also tends to be the smaller child, and the smaller the child, the more careful we must be as their safety margin - the area between sedation and overdose - becomes narrower. These patients are often the ones that go from uncontrollable to unresponsive with minimal changes of sedation, i.e. kicking, screaming, biting, scratching one moment and unconscious and unresponsive the next, with concentration changes of nitrous of only a few percentage points. Our oral medications often come in unit dosages that are not easily divided to provide a more accurate dose for any given weight.

It also is amazing to me how many parents do not know their child's weight. Often when we ask them what it is, we are told "somewhere between 20 and 30 pounds." This is a 50% range; we like to be a little more than 50% accurate with our doses of medication. For this reason, it's a good idea to have a scale in the office to check the child's weight.

Unfortunately, most of the very young, small patients are those who need extensive treatment due to baby bottle caries. These children will tend to continue to need extensive treatment as they get older because of their oral conditions and, in many cases, their treatments will be further complicated by family dynamics. For instance, if a child is left on the bottle, it is sometimes because of a very permissive atmosphere in the family where the child's every qualm is indulged. These are the children that get all the candy they want, receive little discipline, and have overprotective, often first-time parents who themselves do not do well in new surroundings. If there is one patient we want to become a good patient, it's the one we'll be seeing on a regular basis for extensive work. These overprotective parents foster overly dependent, insecure children requiring enormous amounts of extensive dental care at a very early age. It is hard to conceive of a worse combination.

Somewhat older children are easier to treat from a sedation standpoint because their size and physiology offer a wider range of safe dosages. Often these children's fears are a result of peer or sibling descriptions of dental treatment ("The dentist has a needle th-i-i-s-s-s big"), cartoons or other TV pro-

grams (who can forget Curley chasing Larry and Mo around a dental chair with a syringe large enough to use on King Kong), and, occasionally, parental phobias or mistreatments. Here's some of a conversation I overheard in a supermarket, "If you do not stop that and behave, I will take you to the dentist and he will give you a shot!" How relieved I was that the family was not one of my patients!

Various forms of oral sedation have been used by dentists to help apprehensive patients. Patient comfort can be achieved by the practitioner who uses anxiolytics, opioids, and nitrous oxide to allay anxiety and apprehension. This also decreases the likelihood of stress induced medical emergencies. The difficulty of using oral agents, however, is the time it takes to get an effect.

How safe is sedation?

Sedation can be performed safely and effectively by dentists with proper training. 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 high enough doses, but only a select few can actually produce a complete state of general anesthesia. However, 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 that fact that nearly all dentistry is elective. It is very rare to face the situation where a life will be lost if treatment is not instituted. 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 to even the simplest procedures. Even administration of local anesthesia has resulted in death. For this reason, the safety of a sedative system is of the utmost importance.

Sedation, 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, the very young and the elderly, the greater the risk over other procedures. Dione reported that overall mortality in the U.S. associated with general anesthesia, based on self-report of oral surgeons, has ranged from 1:860,000 to 1:349,000; however, self-reportings are usually given little credence due to a strong negative biases. 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 (one patient died in a motorcycle accident later in the day of sedation). Only very low risk could be determined for local anesthesia.[3]

The risk of sedation and anesthesia can be dramatically decreased with modern monitoring devices and the use of persons trained in monitoring and administration of 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.[4] 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, although I insist that another adult take their arm for additional support. They should not drive, undertake any task that might be hazardous, be placed in a position of responsibility (i.e. 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 limited to watching TV, and operating the remote control is about as complex a cognitive activity as they should attempt. It should be stressed to the patient that although they may feel normal, their reflexes may still be depressed. They need to take the rest 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 6 hours after administration. This phenomenon is known as a "second peak effect"[5]. 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% 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, some practitioners felt there was reason for some concern even the next day.

Drug selection

Our choice of drugs is guided by consideration of elimination, half-lifes and side effects:

-Brevital (methylhexital sodium), an ultra short acting barbiturate when given intravenously, can take a conscious patient to a patient under surgical general anesthesia and back to consciousness often in less than 5 minutes total time.

-Diazepam, on the other hand, had a

secondary half life of 20 to 50 hours.[6] We must worry about patients who have had diazepam driving, taking alcohol and performing hazardous activities, not only the day of treatment but possibly for several days after sedation.

-Nitrous oxide is so completely eliminated, patients can drive after a relatively short recovery time.

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."***[7]

It is our goal to chose 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. A pain-free state can always be achieved by rendering the patient unconscious, but with a much greater risk of serious complications. I try to keep the patient conscious and treat their apprehension as opposed to rendering them unaware. If I can alleviate apprehension without changing any other of the patient's parameters, I 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 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 (CNS). The effect can be altered by varying the agent. Some agents are more therapeutic than others. In gaining access to the appropriate areas of the CNS, a variety of routes of administration can be used. Ultimately, this access depends on getting the drug into the circulation of arterial blood going to the brain. Since we are treating apprehensive patients, it is important to gain this access with as little pain as possible. Through inhalation, gaseous agents gain access via the lungs; liquid agents may be injected into the venous circulation, sprayed on nasal mucosa, absorbed sublingually, and injected under the skin into underlying muscle or swallowed and absorbed from the stomach and small intestine. Some agents have been administered rectally.

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

control we have of 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. It is obvious that it is impractical to titrate when we must wait for an hour to see the 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 which may be addictive. 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. However, if only one agent is used, the side effects are often more predictable.

In general terms, it is easier (safer) to use a single agent as we then only have one set of side effects to contend with. This, of course, assumes a single agent will provide the needed effect at a concentration where few side effects are present. When Dione looked at combinations used by 264 dentists he found 82 distinct combinations.[8] "The scientific basis for the use of such a diverse group of agents and combinations is unclear."[9]

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% oxygen), they will excrete most inhalation agents via the lungs, thus reversing the overdose. A practitioner must assure that the patient's respiratory system is functioning normally and that their tidal volume is adequate to provide the oxygen they need and remove their carbon dioxide both for their safety and to remove the inhalation agent. It should be remembered that all agents depress the respiratory system to some extent and it is important to have monitors that assure that an adequate exchange is taking place. It is necessary that the practitioner be skilled in assisting respiration should significant depression take place.

Intravenous sedation

With the regulations that are now in place in many states, it is nearly impossible to use intravenous sedation. Many states require a 60 hour course in addition to any training that was received in dental school. These courses have not been taught for a number of years and do not seem to be

coming back. The cost of malpractice insurance to do intravenous sedation is another problem. If the added cost of malpractice insurance is passed on to the patient, it can increase the cost of each appointment $100 to$200.

Intravenous sedation has several advantages to the oral route of administering medication. When giving a drug IV, one slowly titrates the concentration of a drug 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 (primarily fat stores) and then more slowly as the drug is metabolized into inactive forms (in some cases less active forms) or eliminated in the urine or feces.

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 blood stream 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 either the stomach or small intestine. Depending on the time necessary for absorption, it may be necessary to have the patient take the drug at home before coming to the office. However, I prefer to administer the drug in the office because then I know how much was taken, when it was taken, and by whom it was taken. Also, I don't have to worry about the patient trying to drive to the appointment as the drug starts to take effect. Last but not least, should there be a reaction to the drug, the patient is in the office where aid can be administered.

We need a predictable means of determining dosage. Because it will take 45 minutes to one (1) hour to get the desired sedation, we can not easily titrate or alter the dose if a patient is not adequately sedated. Because of the length of time necessary to get sedation, we can not depend on redistribution of the drug to counter its effect. With some intravenous drugs you can give a dose necessary for sedation and within a few minutes have the patient nearly back to normal because the drug concentration in the blood stream has been reduced as the drug is redistributed to other tissues of the body.

DRUG OPTIONS

Historically, many drugs and routes of administration have been used to control apprehension in the dental offices of general practitioners. As stated earlier, insurance companies, state regulatory bodies and other factors have all but eliminated intravenous sedation from the armamatarium of general dentists.

If we trace the history of the other methods of sedation, however, we will see that all is not lost for the phobic patient.

Nitrous oxide

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 bark a shin, 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. This was a major breakthrough when you consider that any dentistry or surgery up until that time was accomplished with no pain control and depended to a great extent on the speed of the surgeon if the patient was to survive the shock of the procedure. Thus, surgeons became known for their speed. But in the quest for speed, accuracy sometimes suffered and more than one assistant lost a digit or two to the surgeon's knife when holding a limb for amputation. Not surprisingly, the fastest surgeons sometimes had a difficult time finding willing assistants.

Ever since Wells' first use of Nitrous oxide in a medical environment, it has been used as a general anesthetic and, more recently, as a sedative on the conscious patient. Its history as a general anesthetic has brought dentistry some criticism. Nitrous oxide is such a weak anesthetic agent, at one atmosphere of pressure, that 80% nitrous oxide is usually considered to be the minimum concentration that will achieve unconsciousness. Even at this concentration, however, it is not possible to render some patients unconscious and if we go to a higher concentration, we begin to encroach on the 21% O2 found in the atmosphere and expose our patients to hypoxia.

The standard of years gone by 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. 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 the safety of the procedure. Today, hypoxic anesthesia would be severely criticized, and rightly so.

Because it 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. In other words, although sedation with nitrous oxide is not adequate for our most 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 with its depressed reflexes and other hazards.

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 matter into the lungs. So long as a 50% concentration of nitrous oxide is not exceeded, there is little chance of general anesthesia or other more minor complications occurring.

The complications that may be 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; however, the patient is definitely uncomfortable and vomiting certainly can be messy.

The euphoria of nitrous may remind some patients of periods when they were sedated for other reasons, which may be traumatic if the occasion was due to a personal tragedy. Patients will occasionally hallucinate; this again 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. I find it helpful to continually 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. This can happen at relatively low concentrations. Some patients describe the sensation of sexual orgasm. It is not all that easy to identify when this is taking place and what is happening. 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 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. These patients do not exchange gasses well in their lungs. Rather than having many small alveoli with the resulting large surface area to exchange gasses with the blood stream, they have fewer large alveoli, often with scarring which thickens the alveolar wall. Carbon dioxide does not diffuse out of the blood stream nor does oxygen enter the blood stream as quickly as is seen in the normal patient. Carbon dioxide levels increase in the blood stream, causing a decrease in pH because of the increased concentration of hydrogen ions. An increase in concentration of bicarbonate ions tends to buffer the effect of this lowered pH, rendering this stimulate, low pH, less effective. These patients depend on low oxygen levels as a primary stimulant to respiration. If we give such a patient nitrous oxide, it tends to depress this secondary system. The relatively high concentrations of oxygen associated with nitrous mixtures, usually greater than 50% oxygen, render this secondary system ineffective and respiration may cease. A further complicating factor has to do with nitrous oxide's tendency to diffuse into closed spaces. The lungs of COPD patients often have large, gas-filled sacks or blebs. If nitrous oxide diffuses into these spaces, it can cause them to enlarge, possibly to the point of rupture.

Should a person be overdosed with nitrous oxide, it is a simple matter of removing the source of the gas and, provided the patient is breathing, they will eliminate the excessive concentration of nitrous oxide.

Probably the greatest chance of complications when using nitrous oxide can be traced to the gasses being switched. I know of 25 to 30 cases where this has occurred. It can happen in several ways: Plumbers may install nitrous oxide and oxygen lines reversed; machines have been reversed by manufacturers; small tanks depend on a safety pin index system. This system has been compromised by having pins displaced from the tank yolk and by practitioners allowing more than one washer to be placed between the tank and the yolk, rendering the pins ineffective.

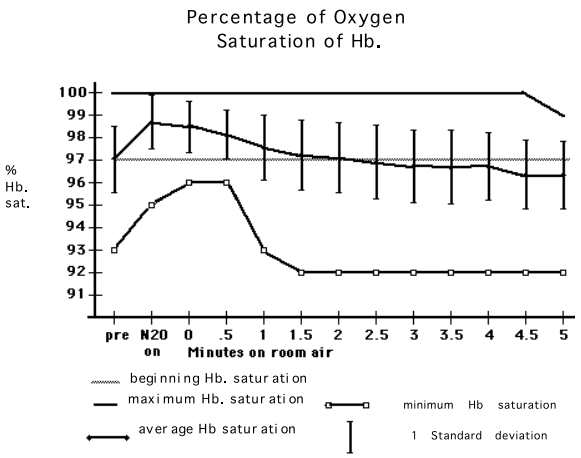


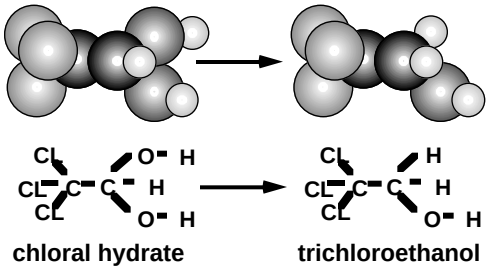
fig. 1. The oxygen saturation of 100 patients increased while on a mixture of oxygen and nitrous oxide. When the patient went back to breathing room air, their oxygen saturation fell slowly over the next 5 minutes. The mean saturations ended up 0.5% below the starting mean but on no patient dropped to a dangerous level. Clinically, diffusion hypoxia was not evident.

It has been the standard to oxygenate the patient for 5 minutes after each nitrous oxide administration to avoid diffusion hypoxia. If oxygenation is continued when gasses are reversed, the patient would be receiving no oxygen and the lack of oxygen will eventually lead to death. In a study we did of over 100 patients, we saw no evidence of diffusion hypoxia. For the healthy patient who uses only nitrous oxide for sedation, there is no reason to oxygenate patients after nitrous oxide.

It should be stressed that nitrous oxide is a very safe sedative for almost all patients.

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 themselves with a bit of liquid reinforcement before coming to an appointment. *It is important when considering the use of other drugs 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.



Chloral hydrate

This drug has been a favorite, particularly for children. In my experience, however, it was very unpredictable. Evidence is now emerging that indicates it may not be as safe as we all believed. Chloral hydrate is a halogenated derivative of acetaldehyde. Its 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. However, a pulse oximeter is advised to monitor as you can get respiratory depression and still have a conscious patient.

Laryngospasm has been reported with 250 mg. Life threatening hypotension and respiratory arrest have been reported in doses exceeding 85 mg/kg. Below 50 mg/kg. there have been few reports of problems. Higher doses tend to induce vomiting, however, thereby lowering the amount absorbed. In one case, although the patient vomited repeatedly starting 5 minutes after an overdose had been administered, they eventually became semi-conscious and suffered cardiac arrest.

In higher doses, chloral hydrate tends to become a cardiac irritant. There have been two reported cases of overdose leading to hypotension. When the hypotension was treated with chatecholamines or agents that released chatecholamines, 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.[10]

Barbiturates

Barbiturates were the standard anti-anxiety agent for both medical and dental patients for many years. This was true even though pharmacologists never claimed that barbiturates dealt specifically with the brain mechanisms responsible for anxiety; they simply 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.

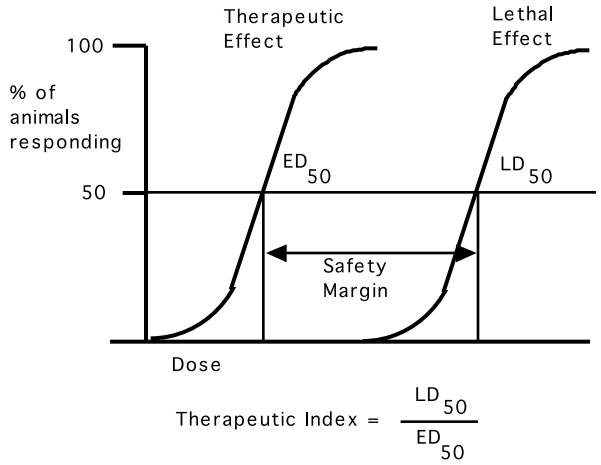


fig. 2. When the percentage of animals showing a therapeutic effect from a drug is plotted against the dose necessary to have the effect, an “S” shaped curve results. A similarly shaped curve results if, rather than a therapeutic effect, the dosage that results in death is plotted. Therapeutic index is derived by dividing ED 50 by LD 50. The larger this number, the safer the drug. With barbiturates, the ratio may be as low as 2 or 3. Benzodiazepine drugs may be as high as 20.

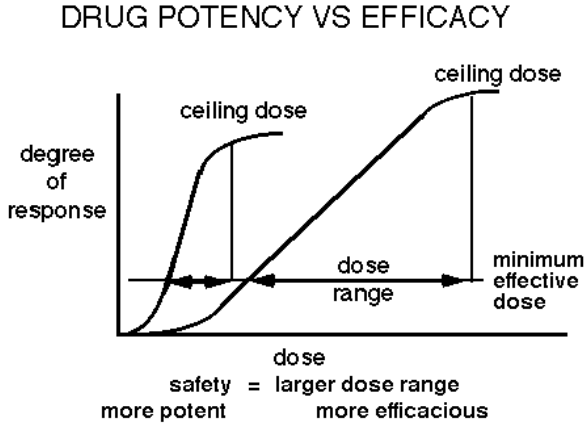


fig. 3. Although the drug on the left is more potent, less drug equals more effect, the drug on the right is more efficacious. The drug on the right is safer as the ratio of minimum effective dose to celling dose is larger.

The ratio of the dose necessary for sleep and the dose that will end in death - the ther*apeutic index* - is usually stated to be a factor of 2 as compared to diazepam with a ratio of 20.[11] Unfortunately, these drugs in higher doses tend to be potent cardiac and respiratory depressants. Because of their addictive nature, they were not administered for long-term anxiety control.[12]

Benzodiazepines

The first step toward developing drugs that act selectively on anxiety mechanisms came about somewhat by chance. In the 1940's a Czechoslovakian pharmacologist, Frank Berger, was attempting to develop synthetic antibacterial agents that would kill microorganisms resistant to penicillin. One group of chemicals, when injected into mice, caused them to become temporarily paralyzed because of a massive relaxation of the muscles in their limbs although they were were fully conscious. In his first publication on the effects, Berger referred to this effect as "tranquilization." He sought derivatives of this original drug, mephenesin, that might be better at controlling anxiety. He found a derivative, Meprobamate, did just that. Meprobamate was introduced to the public in 1955. Although less effective than hoped, it served to introduce the concept of a drug agent capable of dealing selectively with anxiety. The race was on to find such a drug. It is interesting that in later analysis it was shown that Meprobamate was only a sedative; it did not selectively alleviate apprehension. It had, however, stimulated a search for such specific anti-anxiety drugs. As no one knew the mechanism involved, many drugs were tried on an almost random basis to see if any had the desired effect.

Twenty years earlier, in the 1930's, Leo Sternbach had begun a research career in pure chemistry at the University of Kracow, Poland. On the basis of his early research he began a search of a group of chemicals he referred to as quinazolines, but after two years he had failed to show any of the desired effects in this group of chemicals.

A year and half later, while cleaning up his lab, Sternbach found one of the last quinazoline series he had not tested. He gave it to Lowell Randall, Roache's head of pharmacology. This drug turned out to be the most active agent of the group and became known as Librium. Sternbach discovered it was not a quinazoline class, but in the final stages of synthesis had been transformed into a completely different chemical, a new class known as benzodiazepines. From this early success came a number of librium derivatives, the most effective of these, diazepam.

Librium and diazepam do 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.

The most clear-cut advantage of the single agent, benzodiazepine sedation is the fact that overdoses are rarely lethal. In the

case of barbiturates, on the other hand, the lethal dose is only a few times greater than the dose necessary to cause sleep. It is not uncommon when testing benzodiazepine drugs on mice to give doses a thousand times greater than is necessary to cause muscle relaxation and behavioral effects and still have the mice, cats, rats, and monkeys all refuse to die. One should not become overconfident, however, as when added to alcohol or barbiturates, death can result.[13]

To deactivate most oral sedatives we generally must wait for the drug to be excreted or metabolized. In the case of diazepam it is metabolized in liver to another sedative, oxipam, that is available as a long term sedative on its own. Triazolam, along with midazolam, has the shortest half-life of the the benzodiazepine drugs; both are in the 1 to 2 hour range. Midazolam is normally considered to be an intravenous drug although it is beginning to be used orally (mixed in cola drinks) and as a nasal spray. Unfortunately, it has been shown to have a noticeable respiratory depressant effect in higher doses. Triazolam has rapid uptake (about 1 hour to maximum effect), and may be given sublingually for an even faster effect, although it is felt that much of the effect still comes from the drug that is swallowed. It has a half life that is about 1 - 2 hours and very little, if any, cardiac or respiratory depressant effect.

It is this very short half life that makes Triazolam a favorite of mine. The high incidence of retrograde 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.

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 rats) and the concentration that provides sedation (to rats). It is our hope that this ratio is constant for humans. Evidence from self-inflicted overdose emergencies tends to indicate a similar ratio. The self-inflicted overdose patient may sleep for several days but they usually survive if they have not mixed the benzodiazepines with other drugs such as alcohol or barbiturates. The higher the difference between these numbers, the safer the drug. For healthy patients it has been estimated that a lethal oral dose - in absence of any other CNS depressant - must be very large and could be impossible to administer orally.

RESPIRATION

In all cases of dental sedation patients should remain awake. If the patient tends to fall asleep, they should be awakened. It is very difficult if not impossible to tell a patient who has just dozed off from one who is under general anesthesia. General anesthesia, if a person is well trained, has been described as great amounts of boredom occasionally dispersed with moments of stark terror. I cannot recommend too strongly that unless *you are well equipped, well trained, certified (in some states) and have extra insurance coverage to cover*

deep sedation/general anesthesia, you do not want patients to be unconscious and it is not possible to tell physiologic sleep from general anesthesia without trying to wake the person up. If the patient awakes, keep them awake. If they do not awaken, you have a case of general anesthesia and all the risks associated with anesthesia. Your biggest problem and concern will be to assure that adequate respiration continues and that cardiovascular parameters remain constant.

If patients do not easily awaken in response to one's voice, one should evaluate their level of sedation to determine whether they may, in fact, be under general anesthesia or have some medical problem. With some drugs, our concern must be that we have depressed the respiration to the point that an adequate exchange of gas is not taking place. It is not the scope of this discussion to describe the treatment of respiratory depression or arrest. However, 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 assure an adequate minute volume. Skin color has been relied on in the past as a way of assuring adequate tissue profusion. However, the arterial oxygen level can be dangerously low before we see the blue tinge of cyanosis. Anyway, cyanosis is no longer considered to be an adequate monitor of arterial oxygen levels. In this case a pulse oximeter and/or capnograph is invaluable in assessing the adequacy of ventilation.

To properly appreciate the importance of monitoring respiration as well as the advantages of the benzodiazepine drugs, it would be wise to review a topic we all learned in dental school but in all likelihood have not had reason to refer to in our practices. It is with that thought in mind that I offer the following section. This is not intended to be a complete discussion. It should be used as the minimal level of knowledge one can possess and still have some appreciation of what we are doing with the drugs we use.

Physiological basis of ventilation

Ventilation is the movement or circulation of air through the respiratory tract and is the principal component of respiration influenced by depressant drugs. We can control our ventilation by conscious effort, however, our bodies have an exquisite system of sensors, reflexes, and feedback loops to control ventilation involuntarily. The involuntary control originates in the chemosensitive area of the respiratory center located in the ventral portion of the medulla. Metabolic processes of our body produce carbon dioxide (CO2) which is carried dissolved in our blood. When CO2 com-

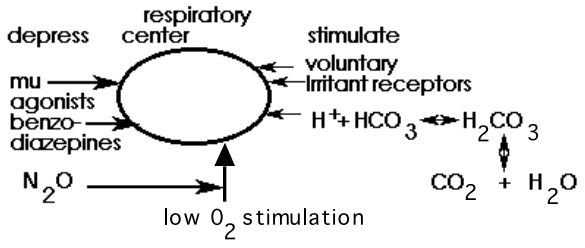


fig. 4. The respiratory center of the midbrain is stimulated by a variety of factors, including low pH due to high CO2 levels, low oxygen levels and irritants. Various drugs can depress these stimulations, including opoids, benzodiazepines and nitrous oxide.

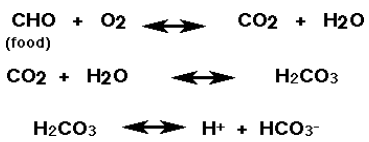


fig. 5. Metabolically, our bodies take food and oxygen and produce carbon dioxide, water and energy. Carbon dioxide and water form carbonic acid that disassociates into hydrogen ions and bicarbonate ions. The hydrogen ion concentrations determine the pH of the blood, the prime stimulus to respiration.

bines with the water in our plasma, it forms carbonic acid which disassociates into hydrogen ions and bicarbonate ions. The negative logarithm of our hydrogen ion concentration determines the pH of our blood. It is this pH which stimulates the chemosensitive region of the respiratory center.

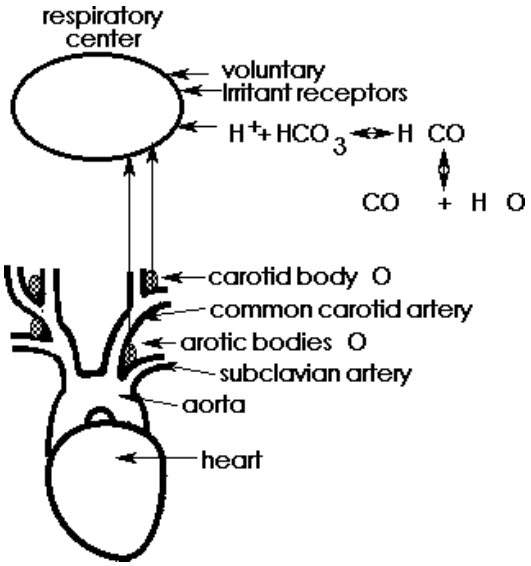


fig. 6. Carbon dioxide stimulation of breathing occurs in the respiratory center of the mid-brain. Low levels of oxygen has an effect on the carotid body and the aortic bodies.

Carotid and Aortic Bodies

The carotid and aortic bodies are closely associated with major arteries of the neck. These harbor other chemosensitive formations sensitive to the low arterial oxygen levels of the blood. Their greatest influence occurs at tension below 60 torr. Because normal levels are well above this value 95-99 torr, these serve as a back-up to the central CO2 sensitive chemoreceptors. Exceptions occur when the central chemosensitive area is depressed by sedative drugs or is tolerant to elevated CO2 tensions that accompany chronic obstructive pulmonary disease (COPD). Ascending impulses from this area travel via the IX and X cranial nerves to the respiratory center.

Respiratory Center

Once the respiratory center is stimulated, impulses travel a short distance to the more dorsally located inspiratory area. This area produces descending neural impulses that lead to the inspiratory musculature causing a contraction of these muscles and inflation of the lung. Once the lung is inflated, stretch receptors ascend to depress the inspiratory area, allowing the inspiratory musculature to relax. This in turn allows the lungs to deflate.

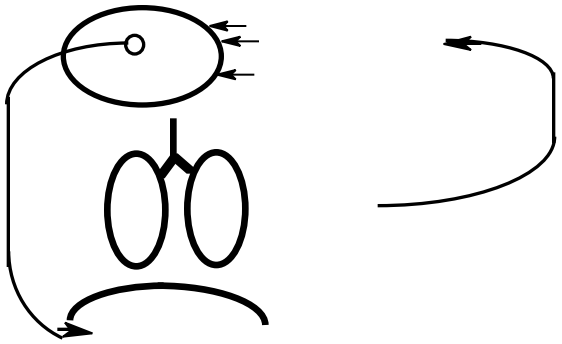


fig. 7. Once inspiratory muscles are stimulated to contract, a negative feedback signal originating in the stretch receptors of the lungs inhibits further contraction of the muscles, allowing expiration of the gasses in the lungs.

Although the involuntary respiratory control is most important during sleep and drug induced sedation or unconsciousness, it is also important in our minute-to-minute functioning while awake. It should be remembered that this system can be overridden by voluntary control. This is important as it allows us to talk. One should not forget that while the patient is conscious ventilation can be controlled voluntarily. Simply stated, a conscious but sedated patient can be told to breathe, should hypoventilation occur.

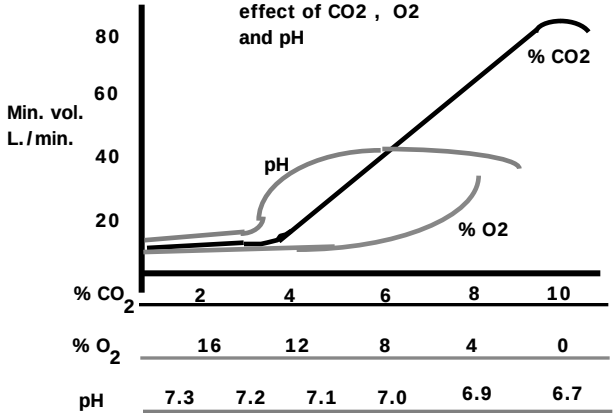


fig. 8. Carbon dioxide, pH and oxygen concentrations in the blood all affect the minute volume of respiration. Carbon dioxide and pH are interrelated, although, because of the buffering capability of the blood, an increased concentration of carbon dioxide does not have a liner relationship with the pH.

CNS depressants can depress ventilation by a number of methods. The opioid drugs - those which stimulate the mu receptors - depress the sensitivity this system has for pH changes. This leads to a situation where the volume of air moved is less for any given concentration of CO2, but as the level of CO2 rises the increase in respiration to this increase is much less than normal (the response curve is "shifted to the right" but the slope of the curve is also depressed). This can lead to high CO2 levels. If the CO2 exceeds concentrations of 10%, it too is a respiratory depressant. The mu antagonists have also been found to depress peripheral hypoxic drive.

Benzodiazepines, in contrast to the opioids, tend to depress the slope of the CO2 response curve but do not appear to shift it to the right. It is fairly difficult to cause serious problems to respiration with benzodiazepines, with the possible exception of midazolam.

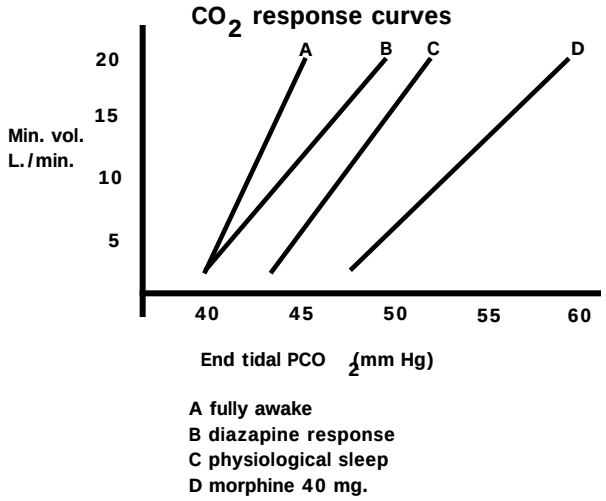


fig. 9. If minute volume is plotted against end tidal CO2, we can see that an increase in carbon dioxide increases the volume of air moved. This increase is depressed by diazapine drugs, sleep and morphine. The morphine effect is greatest as it not only depresses the slope of the response, it also shifts it to the right.

One further drug deserves mention. Subanesthetic doses of nitrous oxide (30% to 60%), such as used for sedation in dental practice, have little if any influence on the CO2 response but have produced a 65% reduction in the hypoxic drive. This could present serious problems if a deeply sedated patient has had CO2 mechanism depressed

by opioid drugs or is a COPD patient.

Monitoring techniques

The solution to the aforementioned problems lies in several areas: (1) Use drugs that minimally depress respiration; (2) Avoid combinations of different drugs that affect several areas at once, and (3) Monitor the patient to assure that adequate arterial oxygen levels are maintained and that CO2 levels do not increase.

Hypoventilation is characterized by a reduction in arterial oxygen tension and an elevation of arterial CO2 tension. With the advent of pulse oximetry, it is now possible to easily monitor oxygen saturation of hemoglobin. Equipment also exists to monitor end-tidal CO2 tension. Although elevated CO2 tension is generally regarded as the earliest sign of hypoventilation, the equipment is extremely expensive.

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% saturation provides reasonable assurance of adequate arterial oxygen tension, 95% is preferred. One should not overestimate the value of this information. Although normal hemoglobin saturation reasonably assures adequate oxygenation, this does not rule out an elevated CO2 tension. If the clinician supplements the patient with enriched oxygen concentrations (as is common when administering nitrous oxide) that may sustain hemoglobin saturation despite hypoventilation. Well oxygenated patients may hypoventilate to the point of significant hypercapnia. Therefore, when using pulse oximetry, oxygen supplementation should be reserved for those cases in which adequate arterial oxygen cannot be sustained, despite verbal commands. This should be a rare event when using light to moderate sedation for ASA I and II patients. By allowing the patient to breathe room air, the oximeter will function more effectively as an early warning of hypoventilation. Although oximetry is not equivalent to capnography, it is valuable in alerting the dentist that ventilation is depressed.[14]

The importance of monitoring a patient's respiration can not be overemphasized. If that patient is awake and responding to verbal commands, we can usually assume our patients are safe. If they are 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. Cheney and Jastak, after reviewing malpractice cases, arrived at the conclusion that airway management represents the most common etiologic factor in brain damage and death in general anesthesia problems. It is the cases of the idiosyncratic reaction, overdose, or the patient on other drugs that were not reported to us that give us the most concern. It is possible for these patients to become unconscious. As practitioners we must be prepared to monitor and assist the respiration of such a patient if it should become necessary. To know if assistance is needed, we

need to know the status of the oxygenation of the patient's tissues.

The Reservoir Bag

In the 1960's, watching the reservoir bag was used on several popular TV programs as a means of determining when it was time to discontinue surgery and give condolences to the next of kin. At least one manufacturer suggested that the presence of a reservoir bag on our nitrous oxide machines could have a negative psychologic effect on some patients. Why do we need one unless it is to monitor the passage of the patient to the great beyond? On the other hand, 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. Fortunately, the lay person's medical knowledge has improved over the years and everyone can now recognize a "flat line" as the determining factor.

Pulse oximeter

The advent of an affordable pulse oximeter has made our life much easier and the patient's life more secure. By passing two different frequencies of light through various tissues, and reading the absorption of the two frequencies and evaluating these differences, this device can determine the percentage of oxygen saturation of the arterial blood with great accuracy. In addition to O2 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. Although not strictly necessary for sedation, the security the equipment provides would be sorely missed if I no longer had a such a device to monitor my sedation patients.

However, there is at least one possible caveat to their use: If a patient is given supplemental oxygen, their hemoglobin saturation will approach 100%. In patients with severe respiratory complications, oxygen saturation could be normal even though exchange rates were inadequate to cleanse the blood of CO2. This could lead to high CO2 levels and resulting low pH of the blood. As was pointed out, however, the patient will be damaged more by a lack of O2 than by high CO2 levels. This potential problem can be circumvented by limiting sedation to patients with no significant respiratory problems.

Capnography

Equipment now exists that constantly senses a patient's expired gas. It then gives a reading of the concentration of CO2 in these gasses. 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. Typically, this equipment indicates end tidal carbon dioxide (ETCO2) concentrations. ETCO2 is the last portion of an expired breath. The concentration of CO2 in the expired gas at the very end of an expiration closely approximates the concentration of CO2 in the alveoli and that of the venous blood. Many machines

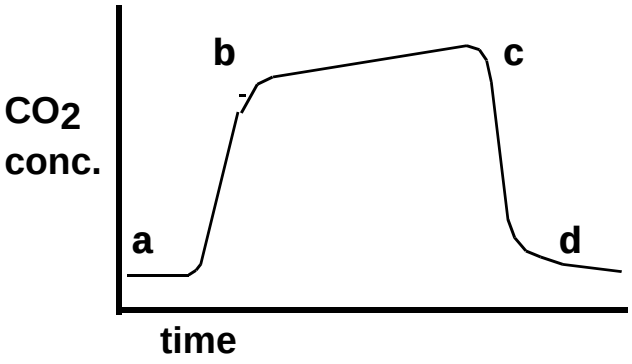


fig. 10. a - exhalation begins, b - c plateau = outflow of alveolar gas, c - end-tidal CO_2 Capnography produces a waveform by continuous analysis of respired gas for CO_2. The presence of the waveform implies exhalation of gases from the lungs. The end-tidal CO_2 (point c) corresponds to alveolar gas which may correlate closely with the $PaCO_2$.

also show graphically the shape of the breath. This can be of interest as it quickly shows a patient who may be taking very long shallow breaths or rapid shallow breaths that could lead to respiratory insufficiency. The shape of the breath also can be an aid in diagnosing some respiratory pathology, including chronic obstructive lung disease and asthma. These machines have alarms that respond to apnea as well as high and low ETCO2 levels, alerting the practitioner when preset parameters are broached.

It is interesting to take a normal, healthy, nonsedated patient and monitor them with the pulse oximeter and capnograpy. Have this patient hold their breath for a minute and watch the reading. The capnograph immediately shows apnea, and the alarm sounds when the apnea has exceeded the preset limit, usually about 20 seconds. At one minute, the pulse oximeter usually starts to show a drop in oxygen saturation, although typically it will still be reading in excess of 95% saturation. Once the patient starts breathing, the ETCO2 will read high until the build up of CO2 has been removed; the oxygen saturation will continue to fall for 30 seconds to a minute. In our trials, however, we were never able to set off the low O2 saturation alarms. The capnograph is a much more sensitive indicator of respiratory depression/cessation.

If our patient is on supplemental oxygen before they hold their breath, the pulse oximeter will normally be reading 99 to 100% saturation and will remain at that level until the person starts breathing again, even though their CO2 levels will have climbed significantly. It is possible to counter the warnings of a pulse oximeter by having a patient on supplemental oxygen.

Cardiovascular Concerns

For our sedation patients, pulse rate and blood pressure should be monitored. In my study and in practice I have a constant pulse rate displayed by the pulse oximeter. In addition, I feel a preoperative blood pressure should be recorded and updated at least every 15 minutes, provided the patient remains awake. Should the patient become unconscious, I would assume they are under general anesthesia or have had some medical problem and I would monitor blood pressure at least every 5 minutes until I have a conscious patient.

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 and does not require any extra equipment to administer. 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.) Patients readily accept oral sedation, although recently some have declined triazolam because of the adverse press it has generated when used as a sleeping pill. Finally, oral sedation is relatively inexpensive for our patients.

Historically, we have used barbiturates and narcotics, both of which have significant effects on respiration and circulation. Diazepam has been used with good effects, but it is slow being absorbed and has a very long half-life. On the other hand, triazolam is a drug that has been around for some time but has been used primarily to aid sleep. In this context, it has received bad press because of side effects that have shown up in patients that use it over an extended period of time. It is the most commonly prescribed sleeping pill used in the US; 7.2 million prescriptions are written annually.[15] It should be emphasized that triazolam is not approved by the FDA as a sedative for dental purposes.[16 17 18]

Triazolam has the advantage of being absorbed rapidly, achieving peak blood levels in 1.3 hours; its half-life is 2-3 hours, much shorter than diazepam.[19] In addition, it may be up to eight (8) times more effective as a hypnotic than diazepam. Yet, triazolam has very little effect on the circulatory or respiratory system. Several studies have shown no changes in blood pressure, pulse, or percentage of oxygen saturation and only a slight change in respiratory rate.[20 21 22 23 24 25] It is metabolized in the liver by the P450 mixed function oxidase system on the smooth endoplasmic reticulum. It is excreted 90% in the urine, 9% in

fig. 11

Benzodiazepine Elimination

drug	time to peak plasma conc.	elimination half-life	major active metabolites
alprazolam Xanax	1-2 hr.	12-15 hr.	α-hydroxyalprazolam
diazepam Valium	0.5 - 4.0 hr.	20-70 hr.	desmethyldiazepam (oxepam)
lorazepam Ativan	1-6 hr.	10-18 hr.	none
midazolam Versed	*	2-5 hr.	none
oxazepam Serax	1-4 hr.	5-15 hr.	none
triazolam Halcion	1- 2 hr. §	1.5-5.0 hr.∞	α-hydroxytriazolm

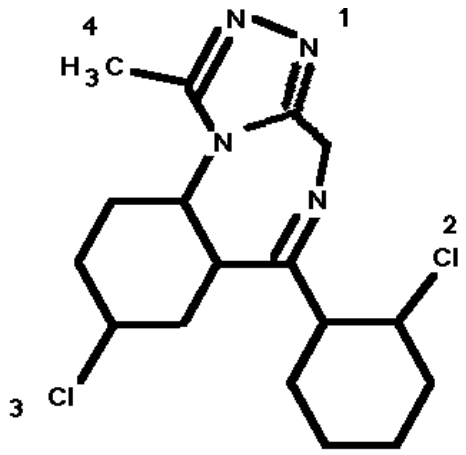
§ peak concentration is 28% faster if given sublingually
∞ half life will be prolonged in the presence of erythromycin, cimethidine (tagamet), isoniazid and possibly oral contraceptives
* not available as an oral agent

the faeces. Its metabolites are not sedative as is the case with diazepam. It does react adversely when taken with a popular ant-acid, cimetidine (Tagamet), which inhibits the P450 system of the liver.

PHARMACOLOGY

Structure-activity relationship

The unique properties of triazolam are attributed to its chemical configuration. The nitrogen atom prevents it from being water soluble. Medazolam 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 it 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 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 it more potent.[26]



Triazolam

1. **This triazo ring is not basic. No water solubility vs. midazolam with a C at this position**
2. **Cl is responsible for increased potency - 5 times that of alprazolam (no Cl)**
3. **Cl is necessary for benzodiazepine action**
4. **Triazolo ring and methyl group responible for rapid oxidation by liver**

fig. 12. If we look at the triazolam molecule and compare it to other benzodiazepine drugs, the location of several effects can be determined. 1. The triazo ring is not basic as is the ring in midazolam which has a carbon at position 1. Carbon in this position makes the midazolam water soluble. The chlorine atom in position 2 makes the triazolam 5 times more potent than alprazolam, which is identical with the exception of this chlorine. Chlorine is necessary in position 3 for the axiolitic action. The triazo ring and the methyl group are responsible for the rapid oxidation of this drug by the liver.

Absorption

Triazolam reaches a rapid peak within 1.3 hours,[27] faster in the elderly and in young women.[28] This occurs more rapidly in daytime than at night, due to longer predose fasting period and is as much as 2 times quicker after a 12 hour fast. [29] Eighty-five percent (85%) is absorbed into the blood stream, 15% passes through in the faeces. It is absorbed 28% faster if given sublingually where some of it is absorbed, but most of it is swallowed.[30]

Distribution

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

Metabolism and Elimination

Triazolam is oxidized in the first pass in the liver by the cytochrome P450-mediated oxidatative system. There have been 6 metabolites identified. Alpha hydroxytriazolam and 4-hydroxytriazolam make up 69% and 11% of the metabolites, respectively. Alpha hydroxytriazolam is 50-100% of the pharmacological activity of triazolam. It is present in the plasma in only very low levels and that which is present is the conjugate form and not active. Triazolam has no active metabolites. Its half- life averages 1.2 to 3.3 hours, but slower at night. Half-life is longer in the elderly because of lower liver oxidizing capacity. There is no change with kidney dialysis but it is slower with cirrhosis. Ninety-one percent (91%) is eliminated in urine and 9% in faeces within 72 hours.[31 32]

Drug interactions

Cimethedine reduces the first pass liver clearance by decreased metabolism and reduction in hapatic blood flow due to decrease in cytochrome P450-mediated oxidatative system. The same effect occurs with erythromycin, isoniazid, an antitubercular agent and possibly some oral contraceptives.[33]

EFFECTS

Central Nervous System

All the benzodiazepines have clinically useful anti-anxiety, sedative-hypnotic, anticonvulsant and skeletal muscle relaxant properties. They all depress CNS to some degree, tending to be more anti-anxiety 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 Gamma Amino Butyric Acid (GABA) receptor complex; GABA alters the chloride ion channels to increase the frequency of their opening. It potentiates GABA. It is now known that there are several GABA receptor sites. Thus, in the future we may have drugs more specific to anti-anxiety with fewer side effects.

Benzodiazepines also interact with the glycine receptors, alter opiate peptide concentrations and 5-HT decreases, a precursor of Seratonin.[34]

Cardiovascular system

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 cardovascular dynamics in doses 4 to 8 times normal.[35]

Respiratory system

Benzodiazepines are respiratory depressants. However, given alone to a healthy

patient they have little effect. They potentiate other CNS depressants. Medazolam is one that can cause respiratory depression and apnea. Triazolam did not depress respiratory response to CO2 in doses 4 to 8 times normal.

Reproduction

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

Recovery

One method of measuring recovery is to have the patient stand with their eyes closed. Patients were normal after 3.5 hours with a .25 mg dose, after 5 hours with a 1. mg. dose, and after 7 hours with a 2. mg. dose. A visual coordination study (following a randomly moving dot with their finger) had patients back to normal after ingesting .25 mg in 5 hours and .5 mg in 11.5 hours. One study using .5 mg had an incident of side effects of 8% sleepiness and 4% headache, dizziness, neuritis, dry mouth.

Mechanisms of action

Benzodiazepines have two current hypotheses of receptor interaction - either a multi-receptor or a single receptor with multiple conformations. GABA (gamma-aminobutyric acid), an amino acid transmitter in the brain, has no known function besides serving as a neurotransmitter and occurs almost exclusively in the brain. GABA reduces the firing of neurons and is an inhibitory neurotransmitter. It is the transmitter at 25 to 40 percent of all synapses in the brain, thus, quantitatively, it may be the brain's predominant transmitter.

Benzodiazepines

Diazepam relieves anxiety, but produces some drowsiness, which is tolerated after several weeks of use. Unfortunately, benzodiazepines are somewhat addicting, with withdrawal symptoms if dosage is stopped. The biggest advantage of the benzodiazepines is the fact that overdoses are rarely lethal. The dose necessary to create problems is many times the therapeutic dose. In this sense, they are among the safest drugs known.

How Benzodiazepines Act

It was established in the 1960's that benzodiazepines and many other sedatives act by affecting the synapse. Cross tolerances were shown with the barbiturates, meprobamate and alcohol. Benzodiazepines act at a different but closely related recognition site. Alcohol, barbiturates and meprobamate all act at the same site. These drugs, as opposed to the benzodiazepine drugs, all put animals to sleep with only modestly higher doses than are required for sedation. This is true in a number of other behavioral tests.

Receptor Sites

It was shown that all these drugs interact with the neurotransmitter GABA. When GABA binds with a receptor site on the neurons, it slows the neuron's rate of firing. The GABA receptor is an integral membrane protein. It extends through the

fig. 13. The most common neurotransmitter is GABA (gamma aminobuteric acid). This chemical is a primary depressant to many synapses of the brain.

bilayered outer membrane of the postsynaptic neuron. GABA has two receptors designated GABA-A and GABA-B. The A receptor changes the ion permeability of the chloride-ion. The B receptor changes the ion permeability of the potassium-ion. In

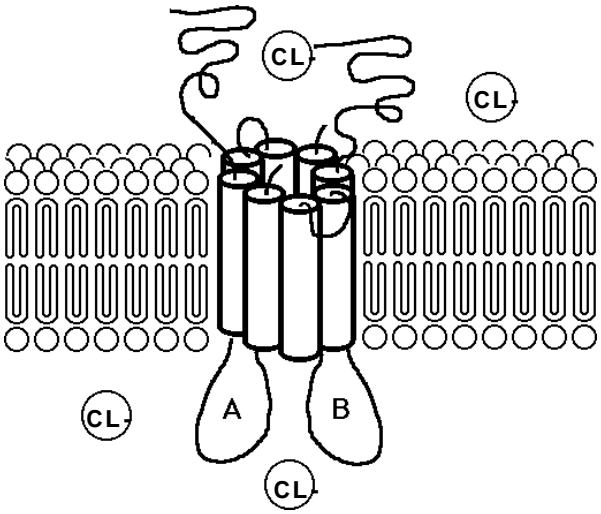


fig. 14. The GABA receptor site is a ring of helictical molecules. This complex has several receptor sites which bind to GABA, benzodiazepine drugs, and other sedatives including alcohol. When these chemicals are attached to the site, the configuration of the helictical molecules change, enlarging the central channel, and allowing calcium ions to enter the cell thereby hyperpolarizing it. This makes depolarization more difficult and inhibits the completion of the synapse.

both instances, the effect is the same. Research in the early 60's showed that inhibitory effects of GABA were potentiated by alcohol, barbiturates, meprobamate and benzodiazepines.

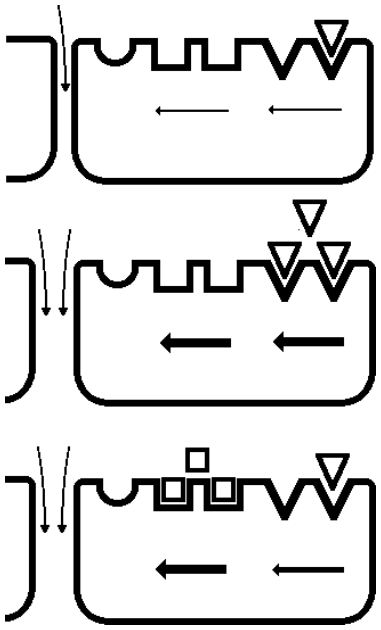


fig. 15. Top: GABA stimulates the opening of the calcium pore. Middle: Greater quantities of GABA open the pore wider. Bottom: Benzodiazepine drugs increase the effectiveness of GABA.

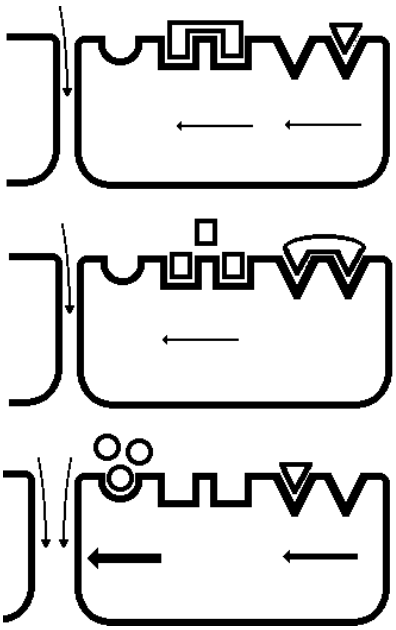


fig. 16. Top: one molecule of GABA simulates the pore opening even with a benzodiazepine blocking agent, flumazenil, in position.
Middle: With a GABA blocking agent in position, benzodiazepine drugs have a diminished effect. Bottom: With alcohol or a barbiturate in position, GABA's effect is increased.

In 1977 two groups showed the existence of specific benzodiazepine receptors in the brain. GABA has similar sites. Benzodiazepines only bind to the GABAs. If either is present, the other's binding ability is enhanced. It is assumed that either effects the shape of the binding site of the other. Both binding sites are on one large protein molecule. Thus, the effects of diazepam are explained by the increased activity of GABA.

The receptor sites are concentrated in parts of the brain that regulate emotional behavior. Within the limbic system, high concentrations are found in the Amygdala. A third receptor site has been shown to exist on the large protein. It is a sedative-convulsant site. This is the site of action of alcohol, barbiturates, and meprobamate and may be effected by drugs that cause convulsions. It was shown that all three sites interact with the other two sites. GABA inhibits synaptic transmission by widening the chloride-ion channels in the neuronal membrane. The receptor site looks much like eight long beads arranged side by side to form a tunnel. Each bead is a molecular helictical structure. Connecting the beads is a linear stretcher strung through the helictical beads which loops from bead to bead. Loops of this material form the A and B sites. It is through the resulting pores that chloride-ions enter the cell. The entrance of chloride-ions into the cell changes the charge across the neuronal membrane making it more difficult for the neuron to depolarize. It appears that the sedative-convulsant site is part of the chloride-ion channel.

GABA increases the size of the chloride-ion channel; the more GABA, the bigger the channel. Benzodiazepines increase the effect of small levels of GABA. Benzodiazepine blockers (flumazenil) do not inhibit the effect of GABA. GABA blockers, however, block the effect of Benzodiazepines. Alcohol, barbiturates and meprobamate, by stimulating the sedative convulsant site, enlarge the chloride-ion channel in the presence of basal levels of GABA. Picrotoxin and other convulsants prevent the widening of the chloride-ion channel even in the presence of large amounts of GABA.[36] [37] It has also been suggested that GABA may influence both dopamine and serotonin levels in the central and peripheral nervous systems.[38]

Contraindications to Triazolam

Before a practitioner uses 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 artificial ventilation as well as assisting 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 be avoided 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.[39] (However, this can often be reversed by pilocarpine.) All the benzodiazepine drugs are tiatrogenic and should not be given to pregnant women. As triazolam has been shown to pass through the lacrimal 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. Because of their depressant effect on the liver mechanisms that metabolize triazolam, it should be given cautiously in patients receiving cimetadine (Tagamet), erythromycin, izonizid and some oral contraceptives.[40]

Relative contraindications

There are 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.

There have been reports of suicide attempts by psychiatric patients. Suicidal tendencies were unmasked, creating this paradoxical behavior.[41] Concurrent drug administration should be avoided as the possibility exists of displacement of other drugs from albumin binding cites.

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 have been reported with doses greater than .5 mg. or when combined with other CNS depressants.

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 they are judged able to leave the office. The patient should not be allowed to sleep at any time while in the office. Vital signs should be taken at regular intervals, every 15 minutes or more often if there is any indication of over-sedation, i.e. tendency to sleep, etc.

Management of adverse reactions should be planned before the drug is used and reviewed on a periodic basis. It should be noted that most adverse effects will 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 Emergency Medical Service by dialing 911 should follow if any doubt exists as to how to proceed.

Protocol in our office

It should be stressed that we do not want a patient who is asleep. If a patient sleeps they are over-sedated and should be kept awake by verbal commands. We do not

worry if 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 may still cry during the appointment. If they are controlled enough to allow dentistry to be safely done, they are adequately relaxed and crying, although distracting to the practitioner, is an indication of adequate ventilation.

Because dental sedation is a new, unreported use of triazolam, I feel we should be extremely cautious. I su*ggest not treating any person who has any medical problem, however slight.*

At a pre-appointment interview, we review medical history to determine that there are no contraindications. At that time, I review with the patient the following points:

They are to have no alcohol or other sedatives for twenty-four hours before the appointment.

There should be no chance that they are pregnant.

They have none of the other contraindications.

They will have an adult take them home after the appointment and stay with them that evening.

As with all sedatives, they cannot drive, operate machinery or undertake any activity that could be hazardous. This includes such activities as walking unaided, climbing stairs, etc.

They should not undertake positions of responsibility, care of children, etc.

They should not make important decisions, legal or monetary, etc., for the rest of the day.

They should not have alcohol or other sedatives for twenty-four hours after the appointment.[42 43 44 45]

The Procedure

The patient comes to the office one hour before we wish to start their dental procedure. I determine the appropriate dose and have them take the triazolam at that time. Many authors have reported on the appropriate dosage for sleep enhancement. Suggested dosages range from .125 mg. to .5 mg.[46 47 48 49 50 51] I administer a dose that is lower than I think will be adequate the first time I treat a patient. An assistant stays in the operatory with them 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 them to assure that they remain awake. I check to see if there is any sign of sedation at thirty minutes. If there is no sedation evident, I 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 forty 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.) I have found that about 75% of patients have amnesia from this point which lasts for 2-3 hours. All patients have had

some amnesia of the appointment.

The dental procedure is started at 45 minutes to 1 hour after administration of the drug. I continue to monitor vital signs and talk to the patient to be sure they are awake.

Once the appointment is complete we keep the patient in the dental chair until they are able to walk and I determine they are able to safely leave the office. Post operative instructions, the same as were given to the patient in the pre-appointment interview (see above), are reviewed with the adult who is going to take the patient home and watch over them the rest of the day. In addition, my home phone is given to this 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.

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

TRIAZOLAM: A CLINICAL STUDY IN A GENERAL DENTAL OFFICE

Introduction

Over a two year period I have used triazolam about 150 times. Forty (40) times were for a double blind study of first time users. This study is yet to be analyzed. One hundred and five (105) uses are reported here. Initially, the patients were monitored by recording blood pressure and pulse. Later, pulse oximetry was added and finally an end tidal carbon dioxide monitor. The first time a patient used the drug we attempted to measure their amnesia. Initially, I feel many of the patients were undersedated. However, we had little guidance as to what dosage to use. Over time, I found sublingual administration could be used at the 30 minute mark where inadequate sedation was inevitable. I now have a dose-weight relationship that I am comfortable with and which rarely fails.

Methods

The patient population included 105 patients of a private dental practice. The mean age was 25.1 years (SD 18.9 years), with a range of 1.5 to 63 years. Average weight was 125.6 pounds (SD 83.7 pounds) with a range of 23 to 286 pounds. 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.

At a pre-appointment interview medical history was reviewed to determine that there are no contraindications to Triazolam. The procedures, possible risks, benefits and options were discussed with the patient or, in the case of children, with their parents. Our office protocol was explained, including the need for an adult to

take the patient home, and the restrictions of their activities on the day of the appointment. It was stressed that we were not attempting to have the patient asleep, although they might experience amnesia for some or all of the appointment.

Patients assessed and recorded their apprehension on an analogue scale graded from 0 to 6. Numbers referred to the following states: 0 calm, relaxed; 1 a little nervous; 2 tense, upset; 3 afraid; 4 very afraid; 5 panicked; 6 terrified. Apprehension was reevaluated at 30 minutes and 60 minutes (the start of the procedure) and at the conclusion of the procedure.

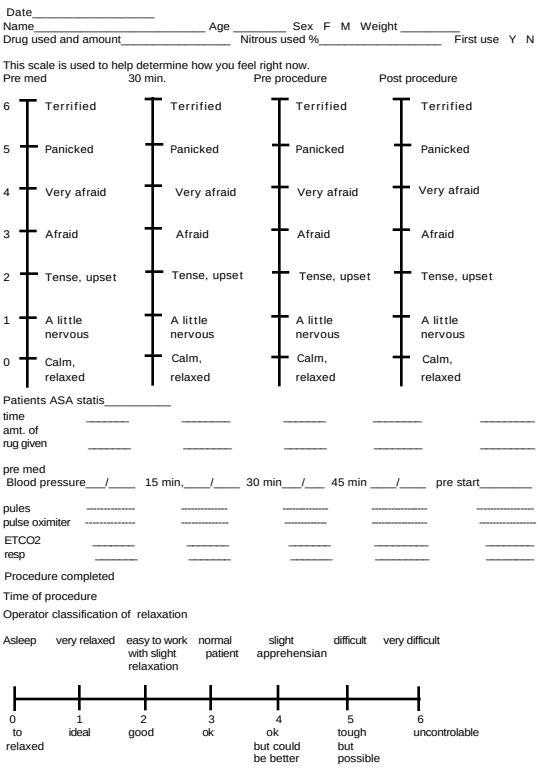


fig. 17. All treatments were recorded on this sheet. Each patient recorded their apprehensions on an analog scale varying from terrified to calm. Numbers were assigned to the various values. At the completion of the appointment, the dentist rated the level of sedation.

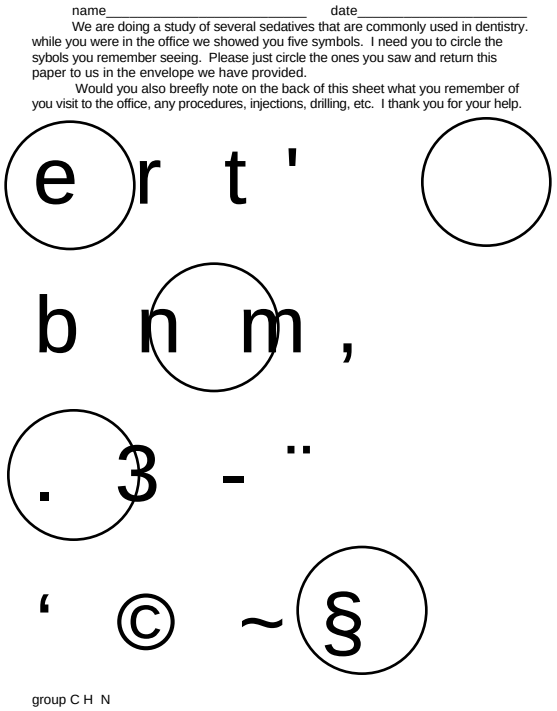


fig. 18. Amnesia of triazolam patients was determined by showing the circled figures and having the patients indicate the following day which symbols they had seen. They also wrote a narrative on the back of this form of what they remember during their appointment.

Twenty-six (26) patients were shown 5 different symbols, one at a time, for 30 seconds. These symbols were shown at the start, at 30 minutes, at 60 minutes, half- way through the procedure, and at its completion. They received a sealed envelope with directions to open it the following day and circle the symbols they remembered from a sheet showing 16 symbols. They also were asked to record a narrative of their memory of the procedure.

Cardiovascular and respiratory parameters measured and recorded included blood pressure (systolic and diastolic), heart rate, percentage hemoglobin-oxygen saturation and end tidal carbon dioxide levels. With uncooperative children, only heart rate and oxygen saturation could be measured. Cardiovascular parameters were re-

corded every 15 minutes until the procedure was started. During the procedure, oxygen saturation and ETCO2 were continuously monitored by a Matrix™ 3700 pulse oximeter and a Matrix™ ETCO2 monitor.

After recording initial data, oral Triazolam was dispensed. Many authors have reported on the appropriate dosage for sleep enhancement. Suggested dosages range from .125 mg. to .5 mg.[52 53 54 55 56 57] Initially, doses in this study were limited to .125 mg. and .25 mg. After several cases of inadequate sedation, I decided to administer one-half the initial dose after 30 minutes if there was no evidence of sedation. Supplemental dosages were necessary for 16 patients. The mean dosage was 0.0042 mg per pound (SD .0022 mg per pound) with a range of 0.00083 to 0.108 mg per pound.

At the close of the appointment the operator assessed relaxation on an analogue scale graded from 0 to 6. Numbers referred to the following: 0 asleep (to relaxed), 1 very relaxed, 2 easy to work with - slight relaxation, 3 normal patient, 4 slight apprehension (crying in the case of children), 5 difficult to work on and 6 uncontrollable.

RESULTS

Patient's apprehension report

Self-reported apprehension levels fell from an initial mean of 3.14 - SD 1.75 (afraid) to 1.97 - SD 1.49 (tense) at 30 minutes and to 1.41 SD 1.45 during the procedure and - 0.85 SD 1.28 (a little nervous) during and after the procedure. The largest drop in apprehension occurred in the first 30 minutes; the second largest drop in the second 30 minutes.

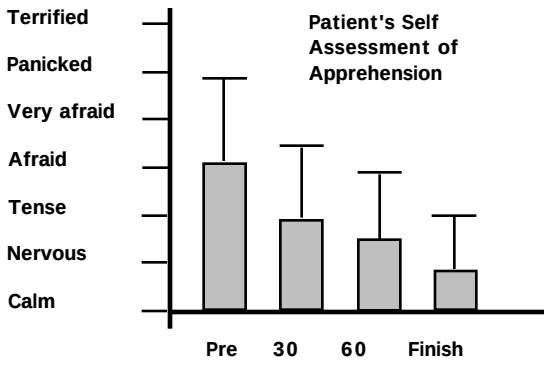


fig. 19. Patients reported their level of apprehension on the analog scale before the drug, at 30 and 60 minutes after taking the medication, and at the conclusion of the appointment. The greatest relaxation had occurred by the 60 minute point. The vertical lines indicate one standard deviation.

Amnesia

All 26 patients remembered the first symbol; 69% remembered the symbol shown at 30 minutes; 50% remembered the 60 minute symbol;40% remembered the symbol shown half-way through the appointment and 32% remembered the symbol shown at the conclusion of treatment. The narratives written by patients tend to agree

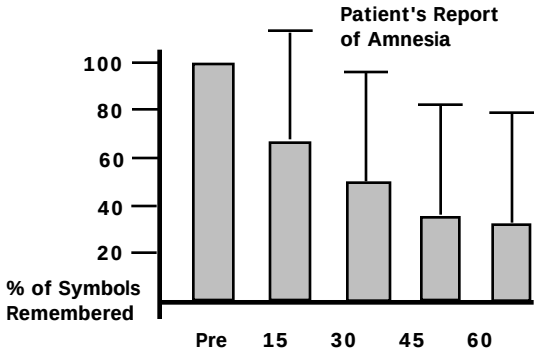


fig. 20. Patients' report of amnesia was about 70% at the start of the dental procedure.

with the amnesia reported with the symbols, 30% remembering the injection which occurred at 60 minutes. Only one patient recalled the whole appointment. Most remembered only small portions of it. A small control group of 3, all normal patients requiring no sedation for dentistry, remembered all 5 symbols.

Cardiovascular-respiratory parameters

Cardiovascular parameters had small changes. The systolic blood pressure fell 9% from a preoperative mean of 124 mmHg - SD l7.6 to 120 mmHg - SD 16.5 at 15 minutes and 117 mmHg - SD 116.7 from 30 minutes to completion. The diastolic blood pressure fell 7% from 79 mmHg - SD 11.7 mean preoperatively to 77.9-76.9 mmHg SD 14.5 - 9.5 from 15 minutes to completion. The heart rate fell from 91.3 beats per minute SD 21.1 to 89.7 SD 19.1 at 15 minutes, fell to 89.0 - SD 18.0 at 30 minutes, climbed to 91.4 SD 20.1 at 45 minutes and climbed to 94.3 - SD 20.7 after the injection of local anesthesia. Hemoglobin-oxygen saturation remained stable at 95.4 - 96.1 % for the whole procedure. End tidal carbon dioxide levels were monitored on the last 11 patients and recorded; it varied from 33.6 mmHg SD 2.7 to 35.0 - SD 2.76.

Dosages

Early dosages derived from reports in the literature for sleep enhancement proved inadequate for our purposes; 16 patients required additional drug. When dose in mg. and weight in pounds is compared

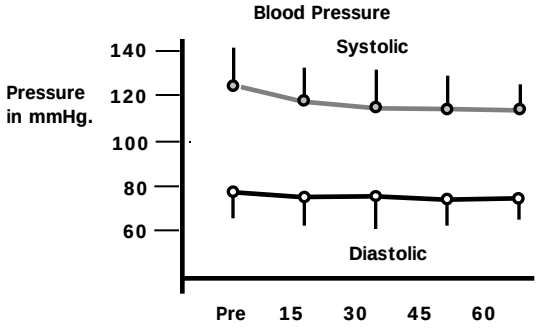


fig. 21. Systolic and diastolic blood pressures both fell slightly after administering the drug. The vertical lines indicate one standard deviation.

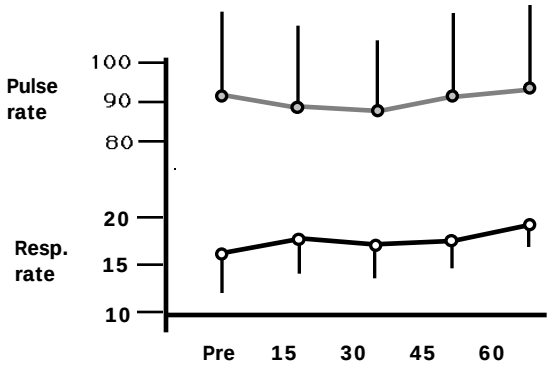


fig. 22. Pulse rates and breathing rates showed very little change. The vertical lines indicate one standard deviation.

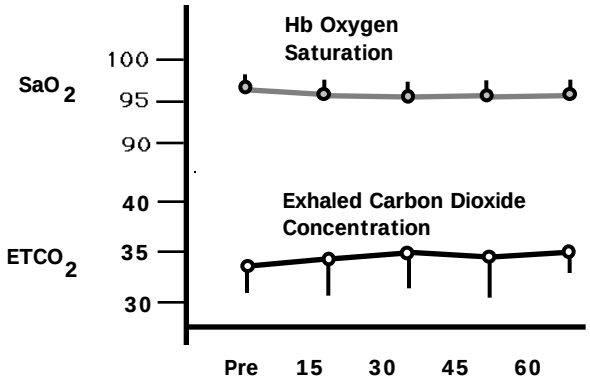


fig. 23. There was very little change in oxygen saturation or end-tidal carbon dioxide levels. The vertical lines indicate one standard deviation. The oxygen saturation data came from 65 uses. The end-tidal carbon dioxide data came from only a few patients (9), however, both indicate that there was little if any change in respiration.

with operator's assessment of level of sedation, a trend emerged indicating that the appropriate initial dosage could be determined by the following equation: Dose in mg. = .25 mg + .125 mg. for every 70 pound weight increment over 40 pounds. In the case of children under 40 pounds, the first treatment was attempted with 0.125 mg. In most cases this dose was ineffective. The mean dosage was 0.0042 mg per pound (SD .0022 mg per pound) with a range of 0.00083 to 0.108 mg per pound.

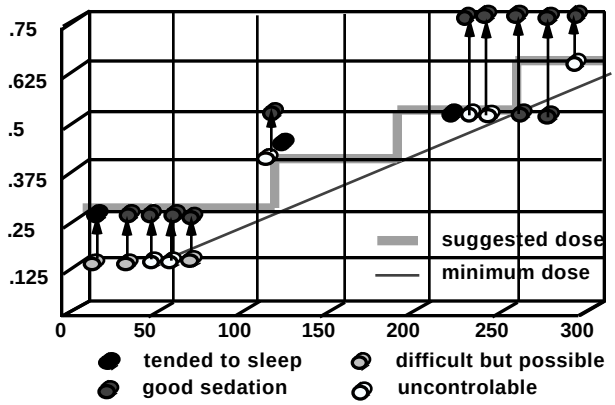


fig. 24. A few patients required higher concentrations of triazolam than what was initially administered. It was these cases that helped to develope the dosage vs. weight relationship that we now use.

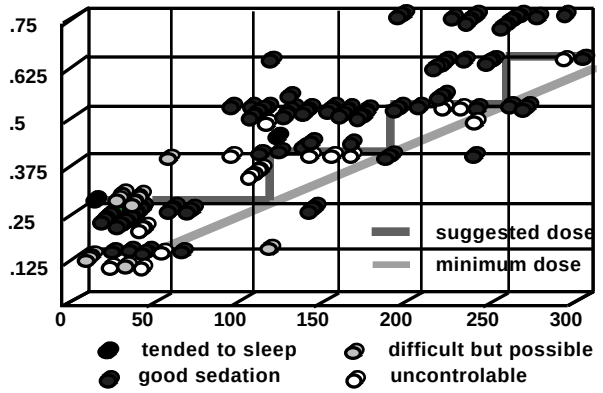


fig. 25. The first 100 patients tended to indicate that the dosage curve I developed is a good place to start. Only three patients tended to sleep, and all three were easily arousable. It should be remembered that all the patients were severely phobic. Moderately apprehensive patients should first be administered a lower dose.

Discussion

It should be emphasized that this study was conducted coincidentally to the patient's treatment in a private practice. The technique described and the parameters evaluated evolved with drug familiarity. As questions arose, the study was expanded to investigate these areas.

With the increased cost of malpractice insurance, it is difficult to justify the use of IV agents for the occasional sedation patient. Oral medication is an alternative. Determining dosage of drug early in the study was difficult. Many of the amnesia failures, higher levels of apprehension and lack of sedation which occurred were with patients who were undersedated because of a lack of knowledge as to what constituted an adequate dose. A much larger study is needed to confirm our findings.

STATUS OF TRIAZOLAM

Upjohn

The Upjohn company distributes triazolam (Halcion) in the U.S. 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 its use for dental sedation and with children is investigational in nature and not supported or encouraged by the company.

FDA

The Food and Drug Administration does not recognize triazolam's use for either dental or pediatric sedation. A practi-

tioner 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, etc. required for prescribing and dispensing a controlled substance. triazolam is a schedule IV substance.

Schedule IV substances "have an abuse potential less than those listed in Schedule III and include such drugs as barbital, phenobarbital ... chloral hydrate ... Meprobamate ... diazepam (Valium) ... alprazolam (Xanax) ... triazolam (triazolam) ... lorazepam (Ativan) ... medazolam (Versed) ... "

To administer, prescribe or dispense any controlled substance a physician (dentist) must be registered with the DEA. "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 manner from all other business documents, retained for two years and made available for inspection by DEA. Controlled substance records maintained as part of the patient file will require that this file be made available for inspection by DEA."

"A physician (dentist) who dispenses controlled substances is required to keep a record of each transaction." "(Dispense means to deliver a controlled substance in some type of bottle, box or other container to a patient. Under these acts the definition of dispense also includes the administering of a controlled substance.)"

"A physician (dentist) who regularly engages in administering controlled substances in Schedule II, III, IV and V is required to keep records if patients are charged for these drugs either separately or together with other professional services. When a physician dispenses a controlled substance and administers this substance occasionally or regularly from the same inventory, the physician (dentist) must keep a record of all transactions." "Administer means to instill a drug into the body of a patient."

Inventory requirements

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

date	.125 mg used	re stock	bal	.25 mg used	re stock	bal	name	sex	weight	age	remarks

fig. 26. The use of triazolam requires an ongoing bookkeeping system. This is a form used in my office. It should be remembered that an actual, signed count is required on a periodic basis.

substances on hand." An inventory of all stocks must be on hand on the date when the use of controlled substances began. "In the event no controlled substances are on hand at the initial inventory, a zero inventory should be recorded."

'The inventory record must:

1. List the name, address and DEA registration number of the registrant.

2. Indicate the date and time the inventory is taken. i.e., opening or close of business.

3. Be signed by the person or persons responsible for taking the inventory.

4. Be maintained at the location appearing on the registration certificate for at least two years.

5. Keep records of schedule II drugs separate from all other controlled substance records."

"All inventories and records of controlled substances in Schedule IV must be maintained separately or must be in such form that they are readily retrievable from the ordinary professional and business records of the physician (dentist)."

Security

"A physician (dentist) who has controlled substances stored in an office or clinic must keep these drugs in a securely locked, substantially constructed cabinet or safe. "

"It is recommended that the controlled substance stock be kept to a minimum."

In my office, the triazolam is kept locked in a key locker which is permanently attached to an office wall. Inventory sheets are kept in a book with patient record forms. This sheet shows date, patient name, age, 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 treat-

ments. They include blood pressure records, pulse rates and pulse oximeter readings. These records are taken and recorded preoperatively and at 15 minute increments from the the drug administration until the case is completed. In addition, the patient reports their level of apprehension preoperatively at 30 minutes, at the start of the procedure (60 minutes), midway through the procedure, and at the close of the procedure. The patient's medical status (ASA rating) is recorded along with their age, sex, weight, amounts of drug administered, name date and whether this is the first administration of this sedative.

Our 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 parameters measured start to change, we should immediately be alerted to this possibility 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.

CASE REPORTS

The reports presented are of my own patients or were reported to me by other practitioners. They represent over 200 cases of sedation and are presented to illustrate the types of problems we have seen and how they were controlled.

The worst case scenario for most sedation is a respiratory depression and/or respiratory obstruction. In this worst case, a patient's exchange of gasses is inadequate to carry adequate O2 to the blood or remove CO2. The levels of O2 in the arterial blood would fall as would the O2 perfussion to tissues, particularly the brain. This depression would allow an increase in CO2 levels and thus a lowering of the pH of the blood. Triazolam has shown very little tendency to depress respiration or affect circulation. Generally speaking, however, and to reiterate my earlier comments, I am concerned when someone tends to sleep since if they are not awake, how do we know if they are under general anesthesia? The most common occurrence precipitating an anesthesia emergency is respiratory insufficiency. For this reason I am more comfortable when working on a conscious patient who is being monitored by a pulse oximeter with the alarm set to go off for any reading below 90% saturation.

Patient No. 1

The first case report is a 34 year old black female ASA 1. She was moderately overweight and had a rather short neck. She had worked the night before her appointment in a manufacturing plant and had been about 36 hours without sleep. I administered our usual dose for her weight.

Thirty (30) minutes later she was noticeably more relaxed. We started her dentistry at 45 minutes and did operative dentistry for about 1 hour. She did fine. Her blood pressure, pulse rate, and respiration were normal. Her pulse oximeters reading ranged between 93 - 97%. At the close of the procedure she tended to sleep if we did not keep talking to her. Several times her head would drop on her chest and she would partially occlude her airway and snore. At these times her SAO2 would slowly fall to 87% over several minutes and she would then take a deep breath and return the saturation to the 93-97% range. We kept her in the dental chair for the next hour until she stopped obstructing and was noticeably less sedated. Her husband took her home with instructions to watch her and call if she had any problems. I called and checked on her several times that evening. She did fine. I was concerned about her obstructing her airway because of her body weight and short neck. Her husband reported that she normally snored when she slept.

Patient No. 2

The second patient was a 40 year old white female. She had been an IV patient for a number of years because of her dental phobia. She was given a modest dose of triazolam. She was noticeably relaxed by 30 minutes and we started her procedure at the 45 minute point. She tended to sleep if left unstimulated but would open her eyes and follow directions if she was spoken to. Her oxygen saturation stayed greater than 95%, her blood pressure and pulse rate stayed constant at pre-operative levels. We kept her in the dental office an extra hour and by that time she was staying awake. She was dismissed to an adult with directions to keep her awake and call if there were any problems.

Patient No. 3

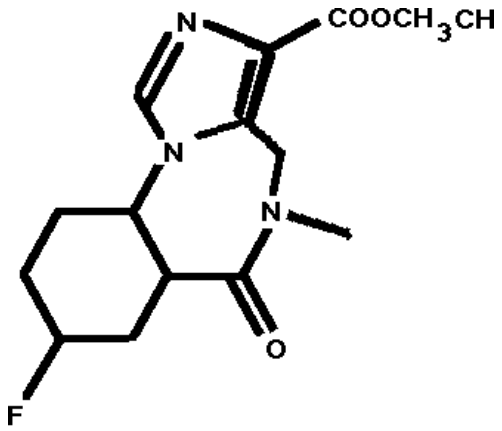
The third patient was a 15 month old, 25 pound Asian female, a recent immigrant who had severe baby bottle caries. Our oral exam was very difficult and was confined to a simple visual exam. We attempted to treat her with 0.125 mg of triazolam as she was nearly uncontrollable. The treatment was somewhat complicated by her lack of understanding of English. We had a parent in the operatory to translate; however, little communication took place due to her age, and lack of control. For the second appointment we used 0.25 mg. of triazolam. She cried and moved some during treatment, but we were able to complete several stainless steel crowns. At the close of the appointment, 100 minutes after administering the drug, she tended to sleep although would awaken if verbally stimulated. Her pulse rate stayed constant at the pre-op levels and her O2 saturation stayed greater than 95% without supplemental oxygen. If left alone, however, she laid very still and slept. Two and a half (2 1/2) hours after drug administration she sat up and told her father she wanted to go home. We again gave directions to observe her the rest of the afternoon and call if she did not stay awake. Her father reported that she went home and watched TV without sleeping.

Patient No. 4

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. 5

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 post-op instructions. At this time she mentioned they would be taking a public 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 assure us that his wife would not have any problem getting him home. We did not insist that the patient be transported by auto.



Flumazenil

FLAMAZENIL MAZICON®

It would be a great advantage to have a drug 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. Because it is impossible to titrate for effect when using oral drugs, it takes a considerable time before it is obvious we have a problem and redistribution and saturation of the other tissues has 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.

History

In 1974, Haefely hypothesized that benzodiazepines act by increasing the effectiveness of the most important inhibitory neurotransmitter, GABA. In 1976 it was shown that diazepam bound selectively to certain brain proteins at the benzodiazepine receptor sites and that they made GABA more effective. They produced several compounds that had a greater affinity for this site than diazepam. One of these, flamezinal, was selected in 1979 as an antagonist for clinical trials.[58]

In early 1992, the Hoffman La Rouche company introduced to the U.S. market a benzodiazepine reversal agent, Mazicon™, flumazenil, ethyl 6-fluoro-6,6-dihydro-5-methyl-6-oxo-4h-imidazo (l,5-a)(1,4) benzodiazepine-3-carboxylate. This agent has been in use in other parts of the world for some time and has proven very important in treating overdoses and reversing the effects of benzodiazepine. Flumazenil displaces benzodiazepine drugs from their receptor site, reversing their sedative action.

Normal dosages of this drug are reported to be .007 and .014 mg/kg. The lethal dose in mice and rats is 62.5 and 125 mg/kg. Another study suggested that 3000 times the therapeutic dose could be given with only minor effects. It has been tested up to 200 mg. given IV and orally. In the case of oral dosages, only 18% are active as it is oxidized in the first pass through the liver.

The following quotation is from a letter from M. L. Bergamo, M.D., Assistant Director, Professional Services, Roache Laboratories, dated February 27, 1992. "Flumazenil is indicated for the complete or partial reversal of the sedative effects of benzodiazepines in cases where general anesthesia has been induced and/or maintained with benzodiazepines, where sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures, and for the management of benzodiazepine overdose."

"Doses of approximately .1 to .2 mg (corresponding to peak plasma levels of 3 to 6 ng/mL) produce antagonism, whereas higher doses of .4 to 1.0 mg (peak plasma levels of 12 to 28 mg/mL) usually produce complete antagonism in patients that have received the usual sedating doses of benzodiazepines. The onset of reversal is usually evident within one to two minutes, with peak effects occurring six to ten minutes after a single intravenous injection. The duration and degree of reversal is also related to the plasma concentration of the sedating benzodiazepine."

"Most patients with benzodiazepine overdose will respond to a cumulative dose of 1 to 3 mg of flumazenil and doses beyond 3 mg do not reliably produce additional effects. On rare occasions, patients with a partial response at 3.0 mg may require additional titration up to a total dose of 5.0 mg."

"If a patient has not responded 5 minutes after receiving a cumulative dose of 5 mg, the major cause of sedation is likely not to be due to benzodiazepines. ... In management of suspected overdose, 497 patients received flumazenil, 299 proved to have taken a benzodiazepine, 83% responded by an improvement in the level of consciousness.

77% responded to a total dose of 1.0 to 3.0 mg.“

“In the event of resedation repeated doses may be given at 20 minute intervals if needed. For repeat treatment, no more than 1.0 (given as .5 mg/min) should be given at any one time and no more than 3.0 mg should be given in any one hour.”

“In the overdose treated patient, reversal of sedation was associated with an increased frequency of symptoms of CNS excitation (agitation or anxiety) which were treated in 1% to 3% of the cases. Serious side effects were uncommon, but six seizures were observed in 446 patients treated with Mazicon in these studies. Four of the six patients who experienced seizures had ingested a large dose of cyclic antidepressants.”

“Resedation has been observed in 1% to 3% of the patients in the clinical trials. Resedation is least likely in cases where Mazicon is given to reverse a low dose of a short-acting benzodiazepine (<10 mg midazolam), and most likely in cases where a large single or cumulative dose of a benzodiazepine has been given in the course of a long procedure along with neuromuscular blocking agents and multiple anesthetic agents.”

Adverse effects

“The most frequently associated adverse events reported during clinical trials were nausea, vomiting, dizziness (vertigo, ataxia), agitation (anxiety, nervousness), emotional lability (euphoria, abnormal crying, abnormal tears), cutaneous vasodilation (sweating, flushing, hot flashes), injection site pain, injection site reaction, fatigue (asthenia, malaise), abnormal vision (visual field defect, diplopia), hyposthesia (sensation abnormal, paresthesia), and headache.”[59]

Mechanism of Action

Flumazenil competitively interacts with other benzodiazepine drugs at the GABA “chloride channel receptor sites in the CNS, particularly in the cortex, limbic lobe, and spinal cord. It has no effect on peripheral receptors.”[60]

Metabolism

“Flumazenil is quickly and completely metabolized in the liver by hepatic microsomal oxidation.” It is converted into inactive acid or glucuronide metabolites. “Less than 0.2% is excreted unchanged in the urine. [61]

Pharmacokinetics

The absorption half-life of oral flumazenil is about 0.3 hours. Peak plasma concentrations occurred 20 to 90 minutes after administration. When given orally the drug is absorbed from the GI system and passes via the portal circulation through the liver before becoming available to the CNS. Only about 16% becomes available to the circulatory system. 200 mg oral doses gave similar blood levels as 40 mg doses given intravenously. Rapid uptake by the brain has been shown to be a 3:1 ratio brain-to-blood. It has been shown to be distributed by the cerebral vasculature and taken up

by gray-matter structures within 1 to 2 minutes if given intravenously. Maximal cerebral concentrations are attained in 5 to 8 minutes. Binding was greatest in the medial-occipital cerebral cortex and to a lesser extent in the cerebellum and pons. It conformed to the GABA receptor sites of the brain and was cleared from the body in 4 hours.[62] [63]

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.[64]

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 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 loraxepam. It should not be given to patients with severe head injuries and unstable intracranial pressures.[65] When given to patients with panic disorder, 2 mg of flumazenil intravenously precipitated panic attacks. It had no effect on healthy patients.[66]

Use with children

Jones administered flumazenil to 40 healthy children aged 3-12 years of age after they had received 0.5 mg per kg orally for premedication and 0.5 mg per kg intravenously for induction of anesthesia. The drug was given along with a placebo and the efficacy of antagonism was assessed. After surgery they were given 0.1 ml (.001mg. of agent) per kg of solution followed by 0.05 ml. (0.0005 mg of agent) per mg per minute until they were either awake or 10 ml. (1 mg of agent) had been administered intravenously. Each 10 ml. of solution contained 1 mg. of flumazenil. Those receiving the active drug awoke approximately four times faster. The mean total dose of flumazenil administered was 0.024 mg per kg (SD 0.019 mg per kg). There were no cases of resedation and minimal changes in the cardio-respiratory variables.[67]

Use with adults

The half-life of flumazenil at 54 (.7 to 1.3 hr, 50 min. average) minutes is less than midazolam and diazepam so you may see some rebound of effect and may need follow-up doses. Sedation was gone within 2 to 5 minutes. One author saw no improvement after 15 minutes, others showed improvement at 15 and 30 but not 60 minutes. One (1) mg will last for about 2 hours. Flumazenil is rapidly eliminated by the liver. Side effects are infrequent but include mild headache, loss of pupil reactivity to light and mild hypotension.

Contraindications

Flumazenil is contra indicated 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 (e.g. control of intracranial pressure or status epilepticus), and in patients who are showing signs of serious cyclic antidepressant overdose.[68]

Resedation

Because of the relatively short half life of flumazenil, 0.8 to 1.6 hours, it is possible that its reversal effect could disappear before the sedative effect of triazolam with its half-life 1-2 hours. Midazolam has a similar half-life (1-2 hours) and several studies have failed to show significant resedation if appropriate doses of midazolam had been used.[69 70 71] Resedation has been shown with diazepam[72] which has a much longer half-life (20-50 hours) and with larger doses of midazolam.[73] Until studies have been reported showing no resedation with triazolam, a patient who requires flumazenil should be observed for several hours after reversal to be positive resedation does not occur. There is a risk that with reversal the patient may feel normal and attempt activities they are not capable of safely performing.

With the introduction of this reversal agent, we will be able to use triazolam with the comfort of knowing that we should be able to 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.

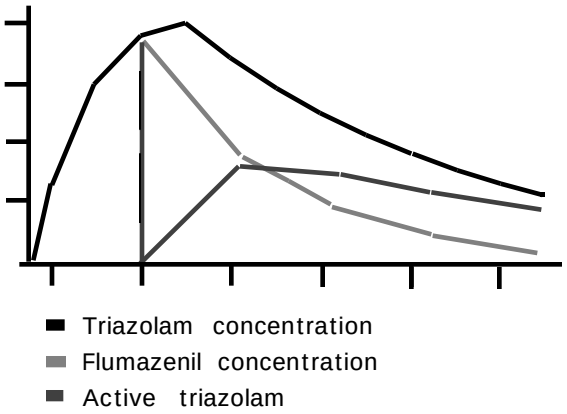


fig. 27.This is a theoretical look at the effect a reversal drug such as flumazinel would have on a triazolam overdose. The bound triazolam would drop to nearly nothing. As the flumazinel, with a half-life of one (1) hr. is metabolized, the triazolam would again be able to bind to the receptor sites; however, the concentration would never reach the pre-reversal levels.

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