Anesth Prog 38:154–171 1991

Adult Sedation: Oral, Rectal, IM, IV

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Conscious sedation is a pharmacologically induced state of relaxation in which the patient remains conscious and cooperative throughout dental treatment. Apprehension, fear, and anxiety are either eliminated or reduced to the point where a previously objectionable procedure, such as dentistry, becomes acceptable. The protective reflexes remain intact, cardiorespiratory parameters are stable, and the pain threshold may be elevated.

Selection of the appropriate technique is based upon the patient's level of apprehension and should be individualized according to the sedative effect required, the need for amnesia, the need for an elevated pain threshold, and the duration of the dental procedure. Sedative medications may be administered singly or in combination, depending on the individual patient and procedural requirements. Single sedatives are useful in managing mild to moderate apprehension levels. Benzodiazepines with specific anxiolytic properties, such as diazepam or midazolam, are the most widely used drugs for this technique. Not all patients however, will respond to a single drug due to the many factors contributing to pharmacologic variability. Multiple-drug techniques may result in less variability in patient response; but with greater potential for drug-induced side-effects and drug interactions.

Whenever conscious sedation is being considered for use in a particular patient, the benefits of the sedation must be weighed against its inherent risks and the risks associated with the body's physiologic response to stress. Catecholamine release during stress may lead to syncope, agitation, excitement, tachycardia, hypertension, and cardiac dysrhythmias. These physiologic and behavioral changes are at best undesirable, and at worst major causes of medical emergencies. Dionne, and others[1] have shown that benzodiazepines attenuate this stress response during oral surgery, thus validating the use of sedation in dentistry. The safety of conscious sedation is exemplary. Ceravolo et al[2] published an 11-year case study of 10,000 patients receiving IV sedation in which there were no major complications. Coplans estimates the mortality rate for parenteral sedation to be approximately 1 in a million.[3] Thus, with its proven benefit of stress reduction and its relative safety, intravenous conscious sedation has a wide variety of uses.

Aside from the obvious use in fearful or apprehensive patients, sedation may be indicated in medically compromised patients, children, gaggers, patients with a history of problems with local anesthesia, and in those requiring surgical or other prolonged dental procedures. An important side benefit of conscious sedation is that it enables the dentist to perform a maximum amount of work in a minimum amount of time.

BALANCING EFFICACY AND SAFETY

When drugs are administered to patients to produce conscious sedation, the observed effects are the culmination of a series of altered physiologic functions. In a true sense, we produce pathophysiologic changes when we administer these agents, some of which are desirable, and some of which are undesirable. Factors which determine how a drug or drug combination will affect the various functions of the human body include: the pre-existing medical condition of the patient, the nature and duration of the present illness, drug interactions, age, nutritional status, environmental factors, and genetically determined factors that may render patients more susceptible or resistant to the effects of a particular drug. In order to maximize the desirable effects produced by these agents and minimize the undesirable effects, a clinician must accurately assess the patient's preanesthetic condition, be thoroughly familiar with the pharmacodynamics of the drugs employed, and be properly trained to continuously monitor the effects produced by these agents. In addition, the clinician should be properly trained to correct any significant pathophysiologic changes produced by the administration of these drugs. The office team should be experienced and well-trained, and there should be sufficient backup resources in the event of an emergency. Without these basic precautions, inadvertent but significant changes in physiologic function may lead to injury or even death.

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ISSN 0003-3006/91/$3.50

Care should be taken to avoid the pitfalls that may lead to an adverse outcome. Without a doubt, the most common cause of anesthetic misadventures is an inadequate preoperative evaluation. This in turn may lead to clinical failure due to improper technique selection, overdosage, or drug interaction. Exposing a medically compromised patient to the risks of deep sedation or general anesthesia when conscious sedation will suffice places the patient at unnecessary risk. Conversely, using conscious sedation when general anesthesia is indicated may lead the practitioner to extend the technique beyond the limits of safe practice. This invariably leads to overdosage, airway obstruction, and cardiorespiratory depression. Inadequate or improper monitoring also contributes directly to anesthetic morbidity and mortality. The mere presence of an electronic monitor does not guarantee the patient's safety. Certain knowledge is required for proper interpretation, and during conscious sedation no monitor should be a substitute for verbally and visually ascertaining the patient's level of consciousness, comfort, and cooperation.

ORAL PREMEDICATION

Oral premedication is generally given first consideration in the management of the mildly apprehensive patient. Because of its ease of administration, convenience, and availability, oral premedication is a popular choice for conscious sedation. The predoctoral dental curriculum offers the training necessary to master this technique, and thus its use is widespread. The availability of a liquid dose form makes oral premedication highly applicable to the pediatric dental patient. It is also a useful modality in patients who are unwilling to accept alternate routes of drug administration. Patients with mask-induced claustrophobia or those with an irrational fear of needles may find the oral route less objectionable.

The primary objective of oral premedication is to reduce anxiety while maintaining consciousness, comfort, and cooperation. This objective is usually met in the mildly apprehensive patient. For the management of the moderately apprehensive patient, oral premedication can be effective when combined with either intramuscular or inhalational agents. However, it is not very effective in extremely apprehensive patients unless intravenous techniques are also used.

Results with oral premedicants are not always predictable since patients may not always follow the prescribed instructions. Also, there is much variability in patient response to oral medication. A full stomach will delay the absorption of oral medication, and thus prolong the onset or produce less than desirable blood levels. Anxiety will delay gastric emptying and produce similar results. The dosages used for premedication are largely empirical and are usually based upon body weight. Unfortunately, this also contributes to a variable response. The advantages and disadvantages of oral premedication are summarized in Table 1.

Table 1. Summary of Advantages and Disadvantages of Oral Premedications

Advantages
— Simple and convenient to use.
— Drugs readily available by prescription.
— Drug reactions are generally less severe.
— Oral route less objectionable than parenteral.
— Requires only minimal training.
— Duration of action may extend into posttreatment period.
Disadvantages
— Patient noncompliance.
— Dosages are largely empirical.
— Titration to clinical endpoint impossible.
— Erratic absorption makes response unpredictable.
— Level of sedation cannot be altered.
— Not useful in extremely apprehensive patients.
— Duration of action may extend into posttreatment period.

Pharmacological Factors Influencing Clinical Efficacy.

Drug Absorption. The overall efficacy of oral premedication is dependent upon the rate and completeness of absorption from the gastrointestinal tract. Lipid-soluble drugs are more rapidly absorbed than nonlipid-soluble drugs, and therefore have a more rapid rate of onset. The rate of absorption is also heavily influenced by the pH of the gastric tissues. The absorption of most oral medications occurs in the small intestine, where there is much more mucosal surface area as compared to the stomach. Therefore, in order to expedite absorption the drug must pass through the stomach and into the small intestine as rapidly as possible. The presence of food in the stomach significantly delays gastric emptying time, and retards drug absorption. Similarly, increased levels of anxiety also delay gastric emptying. This may be one of the reasons why the efficacy of oral premedication decreases as anxiety increases.

Other factors that influence the systemic absorption of oral medication are the dose form of the drug and inactivation of the drug by the liver. The efficient absorption of one dose form over another has to do with the bioavailability of the drug. In other words, only a portion of the dose administered is available to exert its pharmacological effects. Two different formulations of the same drug

Table 2. Drug Absorption Characteristics Influencing the Clinical Efficacy of Oral Sedation

1. Lipid solubility
2. pH of gastric tissues
3. Gastric emptying time
   a. presence of food in stomach
   b. anxiety
4. Mucosal surface area
5. Dosage form
6. Hepatic metabolism ("first pass" effect)
7. Bioavailability

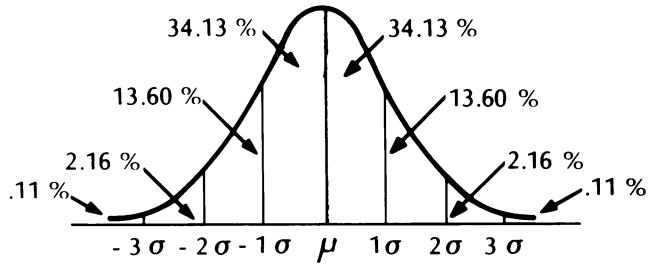
do not necessarily have the same biological or therapeutic equivalencies. Differences in the disintegration and dissolution and differences in the size of the dissolved particles affect their absorption from the GI tract. Liquid dose forms are generally absorbed more rapidly than tablet or capsule forms of the same drug.

Systemic absorption of oral medication is further hindered by hepatic metabolism. Unlike parenteral drug administration, oral drugs are absorbed from the small intestine and transported to the liver via the portal circulation. The drug is subjected to enzymatic degradation before it ever has a chance to reach the active site ("first pass" effect). A summary of drug absorption characteristics influencing clinical efficacy is found in Table 2.

Patient Variability. In an ideal situation, 100% of the population would respond in like manner to a standard dose of any given drug. However, as discussed previously, there are numerous factors that can influence the ultimate patient response. Additionally, even if these factors remained constant, people are going to respond differently to set doses of medication. Patient variability is illustrated by the typical dose-response curve shown in Figure 1.

Assuming a normal distribution of drug sensitivity, approximately 68% of patients will respond within plus or minus one standard deviation from the mean to a drug dose that has been determined to be effective. The remaining population may require more or less than the standard dose, and about 2.5% will either be very resistant or very sensitive to the drug effect. It is no wonder, then, that there is so much variability in the doses required to produce a satisfactory clinical result. Thus, techniques that allow for incremental dose titration to a clinical endpoint are much more preferable than fixed-dose techniques. The limitation of oral premedication becomes obvious.

Figure 1. Typical dose-response curve.



Therapeutic Suggestions for Oral Sedation

One of the most significant problems associated with oral premedication is patient noncompliance. This can make the difference between a successful and unsuccessful dental experience, and may also have medicolegal implications. Since anxiety itself causes noncompliance, it is best to give the patient both verbal and written instructions concerning the oral premedication procedures. These should include not only the type and nature of the medication, but also how much and what time the drug should be taken. A copy of the written instructions should become a part of the patient's permanent record. In order to attain the optimum effect from oral premedication, one should prescribe a dose of medication at bedtime the night before the dental appointment. The same drug that will be used for treatment should be prescribed for this purpose if possible. The dose to be administered prior to dental treatment should be given well in advance of the need. This may be 1 or 2 hours in advance depending upon the medication used. The patient should avoid heavy meals prior to the premedication in order to prevent delays in gastric uptake. Finally, the patient must have a responsible adult to transport him to and from the office. The dentist should prescribe or dispense only the amount of drug that the patient is to take in order to avoid misunderstandings or medication errors. Ideally, the premedicant should be administered to the patient by the dentist in the dental office. This will prevent noncompliance and allow for close supervision as the medication takes effect. These suggestions are summarized in Table 3.

Table 3. Therapeutic Suggestions for Oral Sedation

— Verbal and written instructions should be given
— Bedtime dose encouraged
— Administer well in advance of need
— Avoid heavy meals prior to premedication
— Patient must be accompanied by a responsible adult
— Prescribe or dispense only the amount of drug required
— Doctor-administered dose recommended
— Recovery and assistance may be required

Drugs for Oral Sedation

Benzodiazepines. The benzodiazepines have distinct advantages over other oral premedicants. They are the major drug group with specific anxiolytic properties. If the desired level of sedation is not achieved initially, higher doses may be safely administered at subsequent appointments due to the high therapeutic index of the benzodiazepines. In contrast, higher doses of other agents, such as the opioids or barbiturates, will increase the likelihood of adverse reaction because their therapeutic index is lower.

In addition to their anxiolytic effects, benzodiazepines also have anticonvulsant, sedative, and amnestic properties. Specific benzodiazepine receptors have been isolated in the brain and spinal cord. Their location parallels that of the major inhibitory neurotransmitter in the brain, gamma-aminobutyric acid (GABA), and the major inhibitory neurotransmitter in the spinal cord, glycine. The receptor sites are predominantly found in neuronal surface membranes and are distributed widely throughout the central nervous system. Benzodiazepines intensify the physiologic inhibitory effects of GABA by interfering with GABA reuptake.[4,5]

The termination of clinical activity of the benzodiazepines is determined by the rate of redistribution from the CNS to a peripheral compartment along a concentration gradient. The rate of distribution is reversible and rapid for benzodiazepines since it is dependent upon the lipid solubility of the drug. The elimination phase is irreversible and slow since it is governed by the rate of biotransformation of the drug. For example, the elimination half-life for diazepam is from 20 to 70 hours. In addition, diazepam has active metabolites which produce prolonged sedative effects. The combination of active metabolites and the long elimination half-life accounts for the residual "hangover" effects seen clinically following diazepam administration. In comparison, the elimination half-life for triazolam is 1.5–5.5 hours, which is the shortest for any benzodiazepine. There are also no active metabolites of triazolam. This results in few, if any, residual effects with triazolam.

The benzodiazepines may produce paradoxical excitement. Prolonged sedation may be seen in patients taking cimetidine. Caution in dosing should be exercised in the elderly patient, since they may be highly sensitive to the effects of the drug. Elderly patients may have a decrease in the number of benzodiazepine receptors, impaired total metabolic clearance, and a diminished plasma volume, protein binding capacity, and CNS function. Therefore, drug potency will be enhanced and the dose requirements will be reduced. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma.

Diazepam is the benzodiazepine prototype and is probably the most widely prescribed oral premedicant. It produces reliable sedation and anxiety reduction in most adult and child patients. Its major disadvantage is its prolonged residual effects. The pediatric dose ranges from 0.15–0.3 mg/kg.

Triazolam (Halcion) is a rapid-onset, short-duration benzodiazepine which produces excellent sedation, and often induces sleep as well as a degree of amnesia. It is very useful for pretreatment night-time dosing. Its many advantages make it a drug of choice for adult premedication. Lorazepam is a long-acting benzodiazepine which may produce amnesia following oral dosing. It should be administered 2 hours prior to dental treatment for optimal effect. It is useful for longer dental appointments (3–4 hours), but at the expense of prolonged recovery. Other benzodiazepines used for oral sedation include alprazolam (Xanax) and oxazepam (Serax). The duration of alprazolam results in prolonged residual sedative effects while oxazepam's slow onset limits its clinical utility.

Although midazolam is not available for oral administration in the United States, it is rapidly absorbed from the GI tract following oral administration. The oral dose of midazolam must be approximately twice the parenteral dose since first-pass hepatic metabolism may remove as much as 50–60% of the drug. Its rapid onset and short duration are advantages for its use orally. In one study, an oral dose of 15 mg of midazolam produced acceptable sedation lasting for 45 min in healthy adults undergoing third molar surgery.[6] An interesting side-effect was the production of partial to complete amnesia in 75% of the subjects. It also appears to have value as an oral premedicant in pediatric patients.

Barbiturates. The degree of CNS depression seen with barbiturates is dose-dependent. They may be used to produce both sedation and sleep. However, barbiturates are not specific anxiolytic agents, and although a patient may appear adequately sedated following an oral dose, anxiety may not be relieved. Paradoxical excitement secondary to barbiturate administration is not uncommon, and there may be a decrease in the patient's pain threshold, which may contribute to an already existing patient management problem. Barbiturates may also produce respiratory and cardiovascular system depression and the potential hazards that accompany them. Barbiturates are contraindicated in patients with acute intermittent porphyria and in patients with suicidal tendencies.

Secobarbital (Seconal) and pentobarbital (Nembutal) are usually given in doses of 50 to 100 mg for oral sedation. The pediatric dose for either agent is 2 mg/kg.

Table 4. Summary of Benzodiazepines Used for Oral Sedation (After Greenblatt et al[7])

Drug	*Onset*	*Elimination rate (half-life)*	*Active metabolites*	*Adult dose*
Diazepam	rapid	slow (20–70 h)	oxazepam temazepam desmethyldiazepam	5–15 mg
Triazolam	intermediate	very rapid (1.5–5 h)	none	0.25–0.5 mg
Lorazepam	intermediate	intermediate (10–20 h)	none	1–4 mg
Alprazolam	intermediate	intermediate (12–15 h)	hydoxyalprazolam	0.25–0.5 mg
Oxazepam	slow	rapid (5–12 h)	none	10–15 mg

Histamine-Blocking Agents with Sedative Properties. Histamine-blocking agents all produce mild CNS depression and have anticholinergic and antiemetic properties. The mild CNS depression seen with these drugs makes them suitable agents for combination with other drugs, such as opioids, for oral premedication. Their anticholinergic properties may diminish salivary flow and improve visualization of the operative site. Their antiemetic effects are useful if combinations with opioids are employed.

Antihistamines may produce orthostatic hypotension. Paradoxical excitement and agitation may occur as a consequence of the anticholinergic effects (central anticholinergic syndrome). When used alone, the sedative-hypnotic effect of the antihistamines is highly variable. As a result they are often given (in reduced doses) in combination with other agents.

Promethazine (Phenergan) is rarely used alone as an oral premedicant, but rather in combination with meperidine. The usual adult dose is 25–50 mg, reduced to 12.5–25 mg for pediatric use.

Hydroxyzine (Vistaril, Atarax) is also rarely used alone as an oral premedicant, usually being given in combination with meperidine or a barbiturate. Adult doses range from 50–100 mg; the pediatric dose is 0.6 mg/kg.

Diphenhydramine (Benadryl) may be useful for premedication of an atopic or asthmatic individual. It is also useful for premedication of patients with an "allergic" history to local anesthetics. The dose range for adults is 25–50 mg; the pediatric dose is 12.5–25 mg.

Opioids. The opioids have the desirable pharmacologic effects of analgesia and sedation, which make them useful for oral premedication. However, opioids are poorly active orally, and thus vary greatly in their sedative activity from patient to patient. They may also produce respiratory and cardiovascular system depression which can result in airway obstruction, hypoventilation, and hypotension. When opioids are administered alone and in the absence of pain, they may produce dysphoria instead of the desired sedation or tranquilization.

Opioids may produce GI disturbances such as nausea and vomiting and constipation. Other adverse effects include dysphoria and confusion, orthostatic hypotension, and urinary retention. Opioids are relatively contraindicated in patients with restrictive or obstructive lung diseases.

Meperidine is the opioid most frequently used orally, primarily for pediatric sedation. It is rarely used alone, but rather in combination with promethazine or hydroxyzine. In the authors' experience, a so-called "successful" premedication with meperidine often involves an obtunded child with a compromised airway. It has been reported that most pediatric anesthetic morbidity and mortality is associated with opioid premedication. The usual adult dose of meperidine is 50–75 mg; the pediatric dose is 1 mg/kg.

Alternative Drugs and Routes of Administration. Scopolamine has been proved effective when administered transdermally for the control of motion sickness. It has also been demonstrated to be effective as a preoperative sedative, antiemetic, and antisialogogue via this route.[8] A prepackaged disk containing scopolamine (Transderm-Scop) is applied to the posterior auricular skin on the night before the appointment. Scopolamine is slowly released, and the sedative effects should be evident at the time of the appointment. The antiemetic effects persist up to 72 hours when the disk is worn continuously.

A recent development in premedication techniques has been the use of the intranasal route of administration. Midazolam, fentanyl, and sufentanil have been administered this way to both adult and pediatric patients. It has been shown to be rapid in onset, safe, and highly effective. A fentanyl-coated lollipop has also been used with some success in pediatric patients. Further investigation is justified in this area, as intranasal premedication could be

a useful alternative to the oral route in a wide variety of situations.[9]

Atropine and glycopyrrolate as oral premedicants may be used primarily as drying agents for improved operator visibility. Although atropine crosses the blood/brain barrier and may produce sedation, it should not be considered as a primary agent in this regard.

Atropine, and especially scopolamine, may produce disorientation, confusion, and agitation (central anticholinergic syndrome), and may cause urinary retention. Atropine and scopolamine are contraindicated in patients with glaucoma.

RECTAL SEDATION

Rectal administration of medicines for the purpose of achieving local effects have been used since ancient times.[10] The potential value of this approach has been difficult to fully realize because of inconsistent bioavailability and hence decreased effectiveness of the suppository dosage form.[11–13] The continued interest in the rectal route of administration stems from the difficulty of initiating surgery on an uncooperative patient and from the increasing frequency of surgery performed in the office where sophisticated anesthesia skills may not be available but safe methods of patient management are still needed. Rectal administration of sedative-hypnotics in the infant and child has been the subject of many studies.[14–17] However, the use and efficacy of rectally administered sedative-hypnotics in adults has been infrequently investigated.

The usual candidate for rectal sedation is either a child from 1 to 7 years of age or an emotionally handicapped older child or adult. Less frequently, one encounters the patient who is unable to swallow a tablet and also has a needle phobia. Individuals with a severe physical handicap such as cerebral palsy may also be a candidate for rectal sedation. Rectal sedation for adults in the United States, however, is usually only indicated for patients needing sedation who are unable to be optimally sedated by the oral, inhalation, or parenteral routes.

With the clinical introduction of the benzodiazepines, research and clinical interest was redirected from the use of rectal suppositories to the rectal administration of solutions.[14] Subsequently, many studies have investigated the pharmacokinetics of rectally administered solutions of methohexital or diazepam in children.[15–18] A few studies have focused on the pharmacokinetics of rectally administered diazepam in adults.[19–22]

Rectal Physiology

The rectum, about 10-15 cm long and 15-35 cm in circumference, is empty and flat most of the time. The main blood supply is from the inferior rectal arteries which branch from the pudendal arteries and the middle rectal arteries. Three veins drain the rectum: the superior, the middle, and the inferior rectal veins. The superior rectal vein drains the upper or proximal portion of the rectum. The size of this portion varies among individuals. The superior rectal vein drains into the inferior mesenteric vein and subsequently into the portal vein. The middle and inferior rectal veins drain into the internal pudendal vein and subsequently into the internal ileac vein. The internal ileac vein then drains into the internal vena cava.[10–11]

The blood flow pattern from the rectum is important because the portion of the rectally administered sedative that is absorbed into the middle and inferior rectal veins does not pass through the liver before entering the systemic circulation. This portion of the absorbed sedative does not undergo so-called "first-pass" clearance or elimination. That fraction of the sedative absorbed and carried through the superior rectal vein would pass through the portal circulation. It would therefore be partially cleared by the liver before entry into the systemic circulation like orally administered sedatives. For those agents like meperidine that undergo a large first-pass clearance, the physiology of the rectum may allow a higher serum concentration of a rectally administered sedative than that for an equivalent oral dose. One factor that reduces predictability is that there are extensive anastomoses between the inferior, middle, and superior rectal veins, and some variability in directional flow has been reported.[11]

Dosage Form

The most widely employed dosage form is the rectal suppository. In recent years, evidence has accumulated that a suppository dosage form results in a delayed and much more variable systemic absorption when compared to rectally administered solutions. For example, infants and adults that receive diazepam suppositories experience peak serum levels of diazepam an hour or more after rectal administration while peak plasma levels after a rectal solution occur approximately 20 min following administration.[18,22] The factors affecting absorption of suppositories include particle size, surface properties, drug solubility, as well as any fluid content of the rectum.[11] An additional disadvantage is the relatively fixed dosage format of suppositories.

As a result of the slow and variable absorption patterns, research has been redirected to the rectal administration of solutions and their pharmacokinetics. Recent clinical evaluations in adults of the pharmacokinetics of rectally administered diazepam in solution compared to intravenous diazepam showed similar peak serum levels. The peak serum level for the rectal diazepam occurred only

15 min after that for intravenous diazepam.[19–22] This rapid systemic uptake following rectal administration of sedative solutions results in quicker onset and less variability than the use of sedative suppositories. An additional advantage to solutions is the ability to adjust the dose rather than administering a fixed dose with a suppository. These advantages suggest that rectal solutions hold great promise for a variety of therapeutic endeavors in infants and children; use of rectal solutions in adults is less certain.

Patient Acceptance

In some parts of the world, the rectal administration of medicines for systemic absorption is not widely utilized or accepted. For example, in the United States, the rectal administration of sedative agents is enjoying resurgence among anesthesiologists who treat young children. However, this increase in usage has not extended to the adult population.

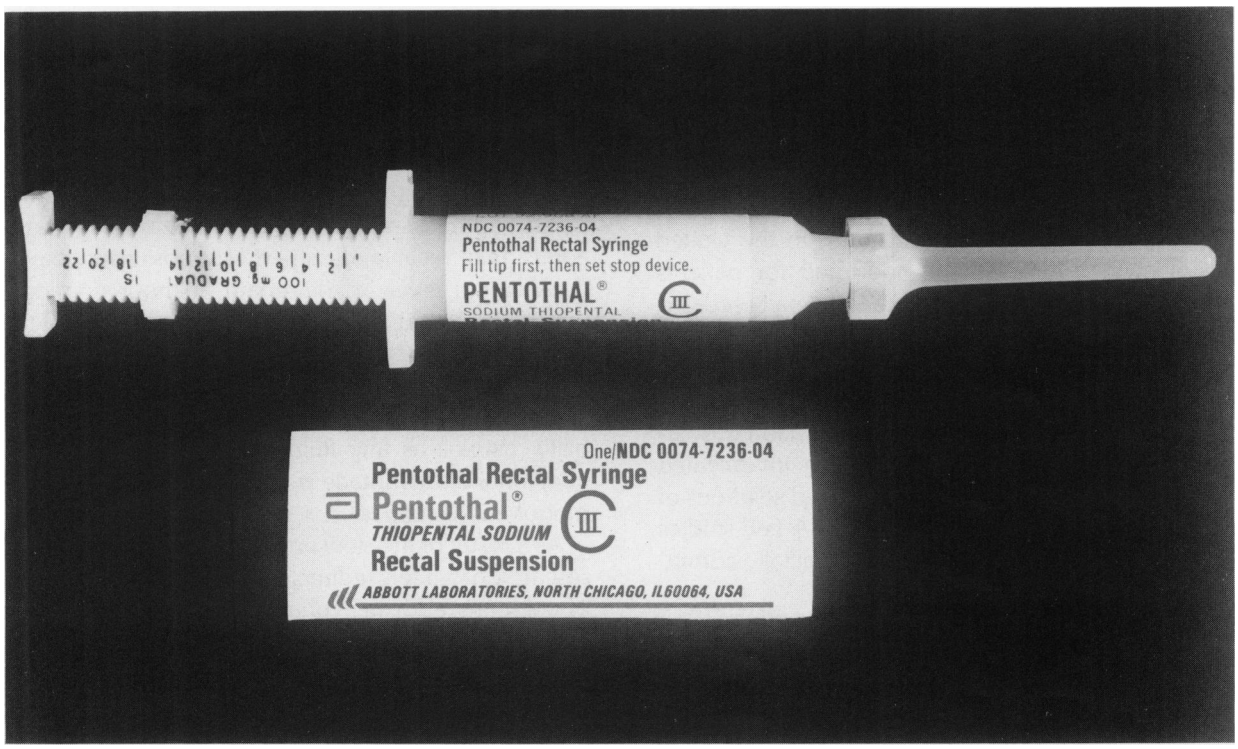
An important application of rectal sedation in adults can nevertheless be identified in the management of the physically or emotionally handicapped adult. This patient population includes those individuals with cerebral palsy, autism, moderate to severe retardation, some patients with Down's Syndrome, some patients with Alzheimer's disease, and other disorders where voluntary patient cooperation cannot be expected. These patients may be institutionalized. Where rectal temperatures are routinely taken, rectal sedatives can be administered and sedation achieved without special cooperation or even the patient's knowledge. This approach minimizes patient disruption, greatly facilitates treatment, and increases patient and staff safety.

Therapeutic Recommendations for Rectal Sedation.

Deep Sedation with Thiopental. The required depth and duration of sedation for dental treatment will depend on the extent of patient anxiety and the procedures to be performed, respectively. Based on considerations previously discussed, it is assumed that the patient is an uncooperative, unpredictable, emotionally labile adult and that deep sedation is the therapeutic objective.

When a short dental treatment time (eg, 15 min) is anticipated, the optimal approach to the uncooperative adult patient is rectal sedation with thiopental in solution. This sedative is commercially available in a prefilled syringe designed for rectal administration (Figure 2). The syringe comes with flared applicator tips, and the desired dose can be set by turning a threaded nut located on the syringe plunger. An effective dose for deep sedation is 44

Figure 2. Prefilled syringe for rectal administration of thiopental.



mg/kg or approximately 10 times the intravenous dose for general anesthesia.

After a flared applicator tip has been adapted to the syringe barrel, the tip is coated with a water-soluble lubricant. The patient is placed in a nonthreatening area and positioned on his left side (if the administrator is right-handed) with the uppermost leg flexed. The individual administering the sedative stands behind the patient where access is better and the patient cannot see the syringe. The tip is then inserted into the rectum, the contents injected, and the tip withdrawn. The patient will generally become deeply sedated and fall asleep within 10 min.

Encountering the dentist and his professional paraphernalia usually makes sedation of the uncooperative patient more difficult. Elevation of patient anxiety can be minimized if the patient has a responsible attendant or family member who routinely takes rectal temperatures. The attendant or family member can and should administer the thiopental after the dose has been set, and the tip adapted to the syringe. If the dentist prepares the syringe and explains the procedure to the attendant or family member while out of view of the patient, then the dentist can remain out of sight until the patient is sleeping. The patient can be told they are going to have a temperature taken. This allows for a much smoother and less traumatic induction of sedation. Once adequate sedation has been achieved, an intravenous infusion should be started, local anesthetic given, and the treatment begun. If after starting it is decided that the treatment cannot be completed in approximately 15 min, then other sedative agents should be given intravenously before the patient becomes awake enough to remove the intravenous infusion line. If it has been determined before starting that the treatment time will be longer than approximately 15 min, sedation can be planned as a multidrug approach with the only goal for rectal thiopental being access to an intravenous infusion. Sufficient anesthesia training to manage deep sedation is a prerequisite for a dentist utilizing rectal sedation with thiopental.

Conscious Sedation with Diazepam. Rectal diazepam has not been widely studied or utilized in the United States in adults or children. However, in other countries, sedation with rectal diazepam in solution has been reported to be well accepted and effective for normal adults undergoing outpatient oral surgery when compared to intravenous sedation with the same agent.[20] The mean rectal dose per kilogram of diazepam is approximately twice that for intravenous administration. Patients sedated rectally achieve lower peak serum levels (71%), higher mean peak desired effects, and have a 50% longer recovery time than those sedated intravenously.[20] It is of note that both routes of administration in this study resulted in a similar incidence of amnesia. Both approaches provided an equal duration of effect as judged by the patient for surgery averaging 33 min. Thus, rectally administered diazepam may indeed represent a practical, longer-acting alternative to barbiturates.[20] One study has reported a small percentage of patients receiving rectal diazepam experienced rectal pain after administration of the agent.[21] Based on its pharmacology, toxicity, and pharmacokinetics, diazepam is very promising as a rectally administered sedative. The lack of an available formulation for rectal use in the United States makes it impractical to make therapeutic recommendations for diazepam at this time.

Suppositories. The use of suppositories is time tested. However, the lack of widespread use of this route of sedation rests in part with the variable bioavailability, consequent variable absorption, and thus lack of dependable clinical effectiveness. The substantial delay to peak effect has reduced its usefulness even more. If, however, a suppository is to be used, a dose must be selected based on a recommended dose per kilogram body weight. If the commercially available product contains too large a dose of sedative, the suppository can be sectioned (eg, cut in half) to obtain the desired dose. The suppository is inserted without additional lubrication in order to avoid delays in absorption. A responsible patient, family member, or attendant can do this at home.

Complications

The most common complication of rectal sedation is the initiation of a bowel movement and passing part or all of the suppository or drug solution. The incidence of this complication is relatively low, but no data are available to provide hard numbers. It would appear to be in the 5% to 10% range.

The most worrisome complication is overdose from the sedatives and the unintended induction of general anesthesia with the potential for airway obstruction by the tongue. This complication is not serious if the dentist is well-trained in anesthesia and is monitoring closely once the patient shows signs of deep sedation. Oxygen via nasal cannula and monitoring with a pulse oximeter are recommended once the patient has achieved deep sedation. A thorough medical history will prevent the administration of thiopental to a patient with a diagnosis of porphyria.

Erosion of the rectal or anal mucosa is infrequently encountered. This can occur when the uncooperative patient tightens the anal sphincter during insertion or withdrawal of the syringe tip.

INTRAMUSCULAR SEDATION

The use of intramuscular injections can be traced back to the middle of the last century when the first hypodermic needle and syringe were developed. Opium was injected along the course of nerves to achieve pain relief. Sedation was a side-effect, the primary purpose being analgesia. In spite of a century of use, relatively little research has been published on the clinical efficacy of intramuscular sedation or, indeed, on the use of intramuscular injections as a route of drug administration.

Intramuscular (IM) sedation is a form of parenteral sedation, ie, sedation requiring a needle for administration. Thus, parenteral drug administration encompasses the subcutaneous, submucosal, intramuscular, and intravenous routes of administration.

The objective of IM sedation is the attainment of an optimal level of patient sedation as quickly as possible without complication and without the establishment of an intravenous infusion. Intramuscular sedation does not have a major role in sedation for dental treatment. Most practitioners select the intravenous route because of the ability to titrate medications or they select the oral route due to ease of use and lack of pain on administration. If the dentist is unable to establish an intravenous line and the patient cannot take sedatives by mouth, IM sedation may then be indicated. Sedation of the mild to moderately retarded, uncooperative dental patient is another example of a possible indication for IM sedation.

Volume of Injection

The volume to be injected usually depends on several factors, including patient weight and the concentration of the sedative in the commercially available product. If the volume for injection is less than 4 mL, the deltoid may be used (Figure 3). If the volume of injection is in the 4-8 mL range, the gluteal, ventrogluteal, or vastus lateralis sites should be utilized (Figures 4 and 5). If the volume of injection is in the 8-15 mL range, then the vastus lateralis site is mandatory. These volume guidelines apply only to the adult patient.

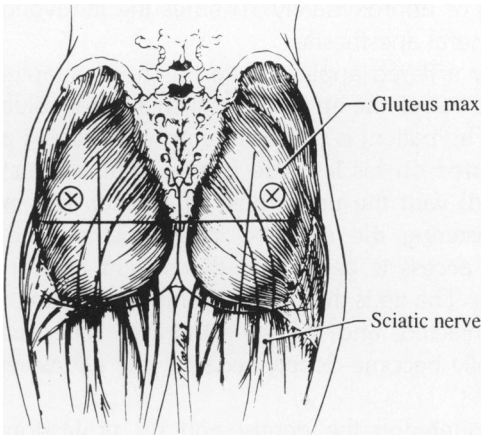


Figure 4. Intramuscular injection site: buttocks (gluteus maximus).

The injection volume that the muscle can tolerate is directly proportional to the muscle size. These guidelines are based on empirical evidence that limiting maximum injected volumes based on total muscle mass minimizes muscle distortion and dissection, thereby reducing pain both during and after injection.[23,24] There is, however, some indirect scientific support for the belief that postinjection pain is proportional to injected volume. Serum levels of a muscle enzyme called creatine phosphokinase (CPK) have been measured following IM injections and confirm that muscle damage is proportional to the volume of injection.[25,26] This enzyme is released after muscle injury. The larger the injury, the higher the serum CPK levels that are observed. It is reasonable to believe that

Figure 3. Intramuscular injection site: shoulder (deltoid).

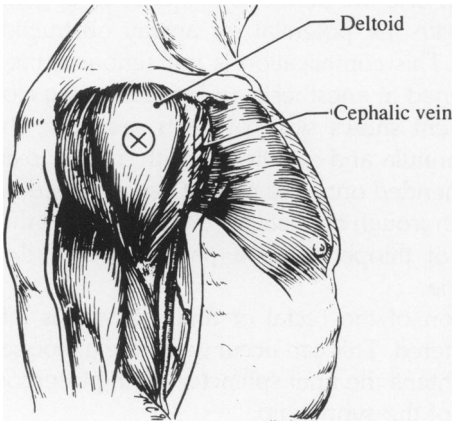
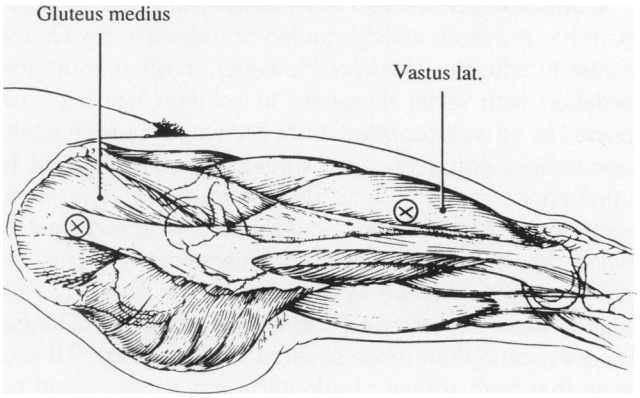


Figure 5. Intramuscular injection sites: buttocks (gluteus maximus) and thigh (vastus lateralis).



postinjection soreness is proportional to extent of muscle damage, which is in turn proportional to injected volume. However, rigid guidelines about limiting injection volume cannot be drawn, as serum CPK levels are also directly proportional to the concentration of the injected solution.[26] When sedating the dental patient, intramuscularly injected volumes greater than 3 mL are rarely necessary. Any of the traditional sites will therefore suffice.

Selection of an Intramuscular Site

Any muscle will suffice for an IM injection. However, there are considerations which have resulted in recommendations that IM injections be routinely made into one of only four anatomic sites.[24] These sites are the gluteal area (ie, the upper outer quadrant of each buttock), the ventrogluteal area (ie, lateral hip), the vastus lateralis (ie, antero-lateral thigh), and the deltoid area (ie, shoulder). Clinical and anatomic descriptions of these areas are available.[24,27] Factors which led to the use of only four sites include: 1) minimal numbers of larger nerve pathways, which reduces the chance for iatrogenic nerve damage, 2) minimal numbers of larger blood vessels which reduce the risk of intraarterial or intravenous injections, and 3) adequate size of the muscle to accommodate the volume of injected solution and thereby minimize pain during and after injection. In medicine, the gluteal area has historically been the preferred single site for IM injections in adults.[23] Specifically, the upper, outer quadrant of each buttocks is recommended because of the lack of large blood vessels and nerves in this area of the muscle. The ventrogluteal area is preferred for bedridden patients.[23] Ambulatory patients often receive IM injections in the deltoid muscle.

Studies of muscle group blood flow utilizing the washout of radioactive materials have demonstrated significantly different perfusion rates (mL blood/100 gm tissue/min) for the four traditional sites for IM injections.[25] The perfusion of the deltoid was determined to be 20% higher than that for the gluteal area, with the vastus lateralis somewhere in between. This is important, because other studies of the pharmacokinetics of IM injections have identified perfusion of the injection site as the rate-limiting step in the absorption of medicines given intramuscularly.[23] When taken together, these observations indicate that onset of sedation is primarily a function of injection site selection. The deltoid muscle thus becomes the preferred side for IM sedative administration in order to minimize the waiting time before surgery can begin.

It is not customary to have a dental patient disrobe for office treatment. Because of this tradition, accessibility at the injection site without disrobing is another factor that should be considered when selecting an IM injection site. The deltoid's accessibility is optimal.

After considering factors such as injection volume, muscle blood flow, onset of sedation, and accessibility, a distinct preference exists for the deltoid muscle for IM injection of sedatives for dental treatment.

Therapeutic Suggestions for Intramuscular Sedation

IM Injection Technique. The skin over the preferred injection site should be cleansed with an antiseptic solution such as isopropyl or rubbing alcohol. A mass of the muscle, for example the lateral aspect of the deltoid, is held with the nondominant hand, allowing the index finger to draw the skin tight by pulling it to the side. The needle is inserted perpendicular to the skin in a thrusting manner to a depth of approximately one inch into the muscle. If extraordinary amounts of adipose tissue are present, a proportionately greater depth from the skin must be used. The syringe is aspirated to assure extravascular needle location, and the contents injected at a modest, smooth rate similar to that for dental injections in the perioral areas. The total time for injection will of course be directly related to the volume injected. Injecting too rapidly causes unnecessary pain. The needle is then quickly removed, and the injected area massaged with a dry gauze for a few seconds in order to spread the injected solution and thereby improve absorption.[24]

The armamentarium for IM injections consists of a sterile syringe, a sterile needle, the sedative to be injected, an antiseptic on an applicator pad, and a dry gauze pad. In an effort to assure sterility, dental and medical practitioners in the United States have discontinued use of reusable syringes and needles for IM and intravenous drug administration. All needles and syringes are now disposable, and this has become the standard of care.

The dentist must be certain of the compatibility of two sedatives before drawing both up into the same syringe. The bioavailability of one or both may be dramatically reduced in some cases as a result of mixing two drugs together.

An effort should be made to relax the muscle into which the sedatives will be injected. It is generally believed that an injection into a contracted muscle is more painful than if the muscle is relaxed.[28] Patient apprehension frequently makes relaxation a challenge.

Agents for IM Sedation. Agents useful for sedation of the dental patient may be selected from the sedative-hypnotic, opioid, phenothiazine, and antihistamine categories of pharmacologic agents. Probably the most commonly used IM sedative in medicine has been a combination of an opioid and a phenothiazine or antihistamine. This probably represents the optimal IM sedation

approach for dental patients as well. Specifically, the combination of meperidine (Demerol) and promethazine (Phenergan) or hydroxyzine (Vistaril) seems well-suited for dental treatment. However, practically any combination of agents from these categories can be found in clinical use. Single agent IM sedation is rarely seen in medicine or dentistry.

The benzodiazepines are not commonly administered as an IM sedative. This appears surprising as diazepam (Valium) has widespread clinical use as an oral and intravenous sedative. Numerous reports suggest that diazepam absorption after IM administration is slower than that seen after oral administration. One study demonstrated that peak serum levels of diazepam occur 60 min after oral absorption and 90 min after IM administration in the leg.[22] Diazepam is also associated with considerable pain during and after IM injection.[29] With the oral route equal or more effective and less painful, the IM administration of the benzodiazepines has not been widely utilized and cannot be recommended. It may be that the newer, water-soluble midazolam will meet with more widespread clinical use an as IM sedative.

Dose selection for any particular adult patient will vary with the health status, age, and procedure to be performed. With the exception of extractions, most dental procedures in which local anesthesia is employed are not significantly stimulating and should not be a consideration in setting dose. After 60 years of age, dose must be progressively decreased. This is especially true for the benzodiazepines.

The optimal drug combination for IM sedation is meperidine (Demerol) 75 mg and promethazine (Phenergan) 50 mg drawn into the same syringe and given as one injection in the deltoid muscle (1.0 mg/kg and 0.7 mg/kg, respectively). This should be effective for the average 20 to 50 year old healthy, anxious 70-kg dental patient needing 1 hour of dental treatment. If the sedation is clearly inadequate 45 min after injection, nitrous oxide and oxygen can be added. If the patient is adequately sedated to fall asleep, 3 L/min oxygen should be given by nasal cannula. Again, advanced age, poor health, or lack of anxiety usually requires a reduction in sedative dose. Onset occurs in about 20 min, reaches a useful therapeutic sedation level in about 45 min and lasts an hour. A useful side-effect of this combination is the drying of oral secretions.

Complications

Complications of IM injections that relate to technique include (1) pain or numbness due to nerve injury, (2) painful inflammatory induration (sterile abscess) in subcutaneous tissues, sometimes accompanied by ulceration of the overlying skin, (3) infection from the use of nonsterile needles, syringes, or contaminated sedatives, and (4) unintentional intravascular administration of sedatives.

Nerve injury is highly unlikely in the deltoid muscle, but is reported in as many as 8% of patients when the gluteal site is injected.[2] Clinically, the patient reports tingling or numbness going down the leg to the foot. It is usually of short duration, but rarely can last months or years. This clinical picture results from injury to the large sciatic nerve, which exits the pelvis into the inner lower quadrant of each buttocks.

Some medications are quite irritating to surrounding tissues and are better tolerated as an IM injection rather than a subcutaneous injection. This improved tolerance may be due to the greater perfusion of muscle and the faster absorption of the irritating sedative. Promethazine and hydroxyzine are examples of irritating sedatives. If the depth of injection is inadequate or some of the drug tracks back to the subcutaneous tissues, an inflammatory response results, and an area of induration can be palpated. This phenomenon is frequently referred to as the development of a sterile abscess. Occasionally, the skin over the induration will undergo necrosis, and an ulcer will also form.

The need for sterile needles and syringes has resulted in the development and widespread use in the United States of disposable needles and syringes for intramuscular injections. The only exception to this is the use of a heat-sterilizable metal syringe apparatus used with disposable needles and glass cartridges similar to that used to administer local anesthetics in dental practices. Use of disposables for IM injections has rendered infection complications quite rare.

Inadvertent intravascular administration is very unusual if the appropriate IM injection technique is followed and the syringe is aspirated before drug administration. Unintentional intravenous administration of sedative should be treated as a potential overdose. Intra-arterial administration can cause loss of limb, depending on the sedative. If the patient is complaining of pain in the limb distal to the injection site and the dentist believes intra-arterial injection was a possibility, the patient should be hospitalized immediately. Aspiration of the syringe before injection will make this complication highly unlikely.

INTRAVENOUS SEDATION

The intravenous administration of drugs for the reduction of patient anxiety represents the last phase in which consciousness is maintained in the continuum from conscious to unconscious pharmacologic techniques. The rapid distribution of drugs when administered by the in-

travenous route overcomes many of the shortcomings of other routes of administration but also introduces greater potential for adverse effects due to overdosage, too rapid administration of an otherwise appropriate dose, or oversedation due to additive effects of drugs given in series. IV premedication became very popular as an alternative to less effective forms of sedation and as a safer modality than general anesthesia. Unfortunately, it was belatedly recognized that this greater efficacy was often accompanied by incidences of serious morbidity and that the use of deeper levels of sedation without proper monitoring carries many of the same risks of general anesthesia. Public and professional concern over the risks of IV administration has led to legislative restrictions to the use of this route of administration and the development of a distinction between conscious sedation and deep sedation. This chapter will be limited to discussion of IV premedication with anxiolytic drugs and adjunctive agents in which consciousness is maintained, protective reflexes are intact, and the patient is capable of responding to verbal instructions and inquiries.

Technical considerations in the use of the intravenous route of administration, such as venipuncture, are beyond the scope of this paper and are readily available from other sources. Other important considerations for the use of the intravenous route discussed elsewhere include monitoring, emergencies, and medicolegal aspects of sedation. While legislative and educational guidelines distinguish between conscious sedation and deep sedation, a clinician administering drugs intravenously cannot be lulled into complacency by nomenclature and must be prepared to manage a patient who becomes less responsive or unconscious. It has been proposed that a main determinant of patient safety during sedative techniques is the choice of the drug, dose, and route of administration, not necessarily the clinical prowess of the administrator.[30,31] Thus, the choice to use IV sedation in clinical practice requires judicious selection of drugs, administration at the recommended rate, limiting the dose to the maximum recommended by the manufacturer, only employing drug combinations when greater efficacy can be demonstrated in comparison to a full therapeutic dose of a single agent, and decreasing the dose of the individual agents when a combination is used. The remainder of this section will focus on aspects of the pharmacology of drugs unique to their use for IV premedication in dental outpatients and on therapeutic recommendations for the use of single agents and combinations.

Drugs Used for IV Sedation

Opioid Analgesics. Opioid analgesics exert their effects primarily through interaction with four major types of receptors found in the central nervous system and in the spinal cord (Table 5). The mu and kappa receptors are associated with analgesia, delta receptors are thought to be associated with alterations in affective behavior, and sigma receptors are involved in the dysphoria and psychotomimetic effects associated with some opioids.[32] Opioid analgesics are classified according to their relationship with the various receptors. The first group, opioid agonists, are drugs which bind to mu, kappa, and delta receptors. The second group, opioid agonist-antagonists, are agonists at some receptors and antagonists at others.

Morphine is the prototype opioid analgesic against which all other drugs in this class are compared. Drugs in

Table 5. Opioid Analgesics and Opioid Receptors

	Receptor			
Drug	*mu*	*kappa*	*delta*	*sigma*
Agonists				
Morphine	++	+		
Meperidine	+	++		
Fentanyl	++			
Agonist-Antagonists				
Nalbuphine	−	+		+
Butorphanol		+		+
Antagonists				
Naloxone	−	−	−	−

Key: ++ = strong agonism
+ = agonism
− = antagonism

this class seem to have preferential affinity for mu receptors, but they are active to varying degrees at the other receptor sites as well.

Opioid agonists exert their primary action on the central nervous system and the bowel.[33] In the central nervous system they produce analgesia without the loss of consciousness, drowsiness, and alterations in mood. Morphine raises both the patient's pain threshold and pain tolerance. During intravenous conscious-sedation, the increased pain threshold, mood elevation, and indifference are valuable commodities to be exploited. Most opioid agonists also produce constriction of the pupil through an excitatory action on the Edinger-Westphal nucleus of the oculomotor nerve. Miosis is pathognomonic of opioid agonists, and no tolerance develops to this effect.

Opioid agonists also produce undesirable effects, such as respiratory depression, nausea, and vomiting. Morphine is a primary and continuous respiratory depressant which affects both respiratory rate and tidal volume. Morphine decreases the responsiveness of the medullary respiratory centers to increasing concentrations of carbon dioxide. The usual ventilatory response to increased carbon dioxide tension is to increase ventilation and return the carbon dioxide levels to normal. The stimulus to breath is obtunded in a dose-related fashion with morphine as carbon dioxide levels rise. If the respiratory depression is significant, patients may be forced to rely on their hypoxic ventilatory drive; that is, they breath only in response to low arterial oxygen concentrations. The ventilatory status must be monitored closely and positive pressure ventilation instituted if necessary.

Nausea and vomiting are at best annoying, and at worst debilitating, side effects of opioid agonists. Although all drugs in this class have the potential for emetic effects, morphine is most commonly implicated. This occurs primarily through direct stimulation of the chemoreceptor trigger zone in the medulla. This dopaminergic effect can sometimes be countered by dopaminergic-blocking drugs such as phenothiazines. There also appears to be a vestibular component to the nausea and vomiting seen with opioids, in that rapid positional changes may induce emesis.

Opioid agonists are cardiovascularly stable drugs that produce no major effect on blood pressure, heart rate, or heart rhythm in the recumbent patient.[33] Peripheral vasodilation does occur, however, as a result of histamine release. Thus, when patients are returned to an upright position, postural hypotension and syncope may occur. Morphine and meperidine promote the most histamine release and are the most likely candidates for postural hypotension. The cerebral circulation is affected indirectly in the presence of respiratory depression. If carbon dioxide levels rise, the cerebral blood vessels dilate, and intracranial pressure increases.

Opioid agonists also have effects on the gastrointestinal tract and other smooth muscle. In the GI system, motility is decreased and smooth muscle tone is increased in the stomach and first part of the duodenum. This causes a major delay in gastric emptying and contributes to opioid-induced constipation. Similar increases in smooth muscle tone occur in the small and large intestines. Biliary tract pressure increases, often with spasm at the sphincter of Oddi. Opioid agonists also increase smooth muscle tone in the ureter and bladder, which results in urinary retention. The volume of urine may also be affected since the secretion of antidiuretic hormone is stimulated. Constipation, urinary retention, and biliary spasm are side-effects to be considered when opioid agonists are used for sedation. In susceptible individuals, these side-effects can override any potential benefit from the drug and should be avoided at all costs. The prudent course of action would be to eliminate them entirely or use a drug in the agonist-antagonist group which is not associated with these effects. The histamine-releasing opioid agonists, morphine and meperidine, may exacerbate or induce an acute asthmatic attack. They also may produce pruritus, sweating, urticaria, and flushing of the face, neck, and upper thorax.

The above pharmacologic properties of opioid agonists apply specifically to morphine and generally to meperidine (Demerol) and fentanyl (Sublimaze), two useful agonists for intravenous conscious sedation. Meperidine was first studied as an atropine-like agent,[33] but it was discovered to have analgesic activity similar to morphine. Meperidine is a weaker agent than morphine; 80–100 mg of meperidine is equivalent to 10 mg morphine. It interacts more strongly with the kappa opioid receptor, and its duration of action is less than morphine. Properties unique to meperidine are its profound antisialogue effect and tachycardia following intravenous administration. A metabolite of meperidine, normeperidine, is associated with toxic effects, such as tremors, muscle twitching, and convulsions. High doses of meperidine may therefore cause an excitatory sequence of events. Meperidine is contraindicated in patients taking MAO inhibitors due in part to an alteration in the rate of metabolic transformation. Inhibition of MAO causes an accumulation of normeperidine which can lead to delirium, hallucinations, seizures, hyperpyrexia, or respiratory depression.

Fentanyl is an extremely potent analgesic which is 80–100 times as potent as morphine.[33] It acts primarily at the mu receptor, and it produces the most profound respiratory depression of the drugs discussed in this class. However, its short duration of action makes it useful as a sedative agent for shorter dental procedures. Fentanyl produces little if any euphoria or mood alteration. It is easy to overdose patients with fentanyl if this fact is not appreciated. Inexperienced clinicians, expecting to see

mood elevation with fentanyl, will readminister the drug until severe respiratory depression occurs. Fentanyl does not produce histamine release and may be used in asthmatic patients, providing that respiratory depression is avoided. Fentanyl has been associated with chest-wall rigidity, or stiff-chest syndrome.[34,35] This occurs through the enhancement of dopaminergic transmission. Although all opioid agonists can do this, fentanyl seems more prone to this effect. Chest-wall rigidity is usually associated with the rapid administration of high doses, but it has been reported with as little as 25 μg of fentanyl.[35] This effect can be antagonized by naloxone.

There are two opioid agonist-antagonists which are useful for intravenous conscious sedation, nalbuphine (Nubain) and butorphanol (Stadol). Nalbuphine is a competitive antagonist at the mu receptor, but it has partial agonist properties at the kappa and sigma receptors (Table 1). Nalbuphine is equipotent with morphine, but in contrast to the dose-dependent respiratory depression seen with morphine, there is a ceiling or plateau effect to the respiratory depression of nalbuphine. Nalbuphine produces no histamine release, minimal biliary constriction, and is cardiovascularly stable.[36]

Butorphanol has little effect on the mu receptor, but it acts as a partial agonist at the kappa and sigma receptors (Table 1). It is a much more potent drug in that 2 mg of butorphanol is equivalent to 10 mg of nalbuphine or morphine. While respiratory depression can occur, it also exhibits a ceiling effect. Butorphanol does not cause histamine release or biliary constriction, but unlike nalbuphine, it increases pulmonary arterial pressure and the cardiac index.[37] The increased work of the heart may preclude its use in patients with significant cardiac disease.

Any drug that stimulates sigma receptors has the potential for psychotomimetic effects. These are described as uncontrollable or strange thoughts, anxiety, nightmares, and hallucinations. These are not common in therapeutic dose ranges, but their incidence may increase with increasing dosages. Both nalbuphine and butorphanol may produce these effects, but it is unlikely in the doses used for conscious sedation. Agonist-antagonist drugs are contraindicated in opioid-dependent patients due to the possibility of precipitating a withdrawal syndrome.

Precautions for Use. Opioid analgesics are contraindicated in cases of closed-head injury where intracranial pressure may be elevated. The carbon dioxide retention that may occur with opioids could further increase intracranial pressure and produce disastrous results. These drugs should also be used with caution in patients with severe restrictive or obstructive pulmonary diseases. Further increasing carbon dioxide levels in patients with chronically elevated arterial carbon dioxide could effectively knock out the respiratory drive. Caution should be used with asthmatic patients as well. Opioids that release histamine, such as morphine and meperidine, could precipitate an acute asthmatic episode during treatment. Therefore, opioids are relatively contraindicated in the presence of respiratory disease.

Drug interactions between opioid analgesics and other drugs may be cause for concern. The central nervous system, cardiovascular, and respiratory depression associated with opioids can be potentiated by benzodiazepines, phenothiazines, tricyclic antidepressants, and MAO inhibitors. Dosages should be appropriately reduced in these instances. The combination of meperidine with an MAO inhibitor is potentially life-threatening and is to be avoided.

Benzodiazepines. Although benzodiazepines used for IV sedation have a high margin of safety, their clinical effects are highly variable. They must be carefully titrated to clinical effect rather than administered as a bolus injection. Midazolam (Versed) has twice the affinity for the benzodiazepine receptor as diazepam (Valium).[38] This accounts in part for the higher potency and greater amnestic and anticonvulsant effects of midazolam.[39] Both diazepam and midazolam produce respiratory depression in a dose-related manner by decreasing the ventilatory response to carbon dioxide. This respiratory depression is markedly worsened when midazolam is used in patients with chronic obstructive lung disease.[40,41] In contrast, when diazepam and midazolam are slowly titrated intravenously to a fixed clinical endpoint, no clinically significant ventilatory changes occur.[42,43]

Diazepam and midazolam have little effect on hemodynamic stability. Glisson et al[44] found that midazolam suppressed plasma elevations of epinephrine and norepinephrine during induction of general anesthesia. This indicates that midazolam, like diazepam, may be of value in attenuating catecholamine surges during stress.

The pharmacokinetic profile of the benzodiazepines conforms to a classic two-compartment model; that is, distribution from a central compartment to a peripheral compartment along a concentration gradient, and then elimination. The distribution phase is reversible and rapid for benzodiazepines. The elimination phase is irreversible and slow since it is governed by the rate of biotransformation of the drug. Termination of activity for the benzodiazepines is caused by a combination of redistribution into the tissues and metabolic biotransformation.

The extreme lipid solubility of midazolam produces a very rapid onset. The distribution half-life for midazolam is 6–15 min. The short duration of action of midazolam is attributed to its very high rate of metabolic clearance and rapid rate of elimination. The elimination half-life for mi-

dazolam is 1–4 hours, which is faster than that of other benzodiazepines. In addition, the metabolites of midazolam are mostly inactive.[45]

Diazepam has a slower rate of distribution than most benzodiazepines (half-life = 30–66 min), and therefore has a somewhat slower (twice) onset than midazolam. The elimination half-life for diazepam is 24–57 hours, which is at least 10 times slower than for midazolam. Diazepam also has two active metabolites, desmethyldiazepam (elimination half-life = 41–139 hours) and oxazepam, which both produce sedative effects.[45] Termination of clinical activity for diazepam occurs primarily through redistribution. However, the combination of active metabolites and the long elimination half-life accounts for the residual "hangover" effects seen clinically following diazepam administration.

A number of factors influence the pharmacokinetic profile of the benzodiazepines. For example, the elimination half-life for diazepam and midazolam is prolonged in the elderly patient due to an impairment in the total metabolic clearance rate.[46] The number of benzodiazepine receptors may also be decreased. Therefore, the dose requirement for diazepam and midazolam is lower in the elderly patient.

The extremely obese patient also presents as a management problem, because the elimination half-life of both diazepam and midazolam increases along with the volume of distribution. However, higher than usual dosages may be required to counteract the rapid redistribution of the drugs into fatty tissues. Thus, in the obese patient, higher drug doses may be necessary to produce the desired effect, and the recovery period may likewise be more prolonged.

A decrease in plasma proteins, especially serum albumin, as is often seen in renal failure, results in an alteration in protein binding capacity. Since the benzodiazepines are highly protein bound, renal failure could increase the free fractions of midazolam and of diazepam and its metabolites. This could result in more profound and prolonged effects. Therefore, the dose of diazepam and midazolam should be reduced in patients with chronic renal failure.[47]

Therapeutic Suggestions for Sedation with Benzodiazepines. Diazepam and midazolam have been used extensively as primary agents, and in conjunction with opioids, for intravenous sedation. The properties of diazepam and midazolam are compared in Table 6. Diazepam is not water soluble, and is therefore dissolved in a vehicle containing 40% propylene glycol. This vehicle has been implicated in a significant incidence of pain during intravenous injection and venous irritation. The long elimination half-lives of its two active metabolites tend to prolong recovery by producing residual sedation and "hangover" effects. Despite these negatives, diazepam has been the mainstay for years as the principle drug for intravenous conscious sedation in dentistry. Its safety record has been remarkable, and it is decidedly less expensive than midazolam.

Table 6. Midazolam Versus Diazepam

Property	*Midazolam*	*Diazepam*
Water solubility	Yes	No
Pain on injection	No	Yes
Venous irritation	< 1%	5–30%
Distribution half-life	6–15 min	30–66 min
Elimination half-life	1–4 hr	24–57 hr
Metabolites	Inactive	Active

Compared with diazepam, midazolam has some significant advantages. Because it is water soluble, there is little or no pain during intravenous injection, and the incidence of venous irritation is virtually nonexistent. Midazolam has a more rapid onset and produces more profound sedation and better amnesia than diazepam. Although patients who receive midazolam may be slightly more somnolent at the end of a procedure, and the return to "street fitness" may be slightly longer,[48] the short elimination half-life and the lack of active metabolites make overall recovery from midazolam sedation extremely rapid when compared with diazepam. With all else being equal, the water solubility and short elimination half-life of midazolam make it the superior drug for intravenous conscious sedation for outpatient procedures.

The recommended dose range for intravenous conscious sedation with diazepam and midazolam is 0.15–0.3 mg/kg and 0.05–0.075 mg/kg, respectively. However, a more appropriate method of sedation with diazepam and midazolam is slow titration of the drug until a predetermined clinical endpoint is reached. Cardiorespiratory depression should be absent when this titration method is used. Should readministration become necessary, 25% of the initial dose of either drug will generally return the patient to the baseline level of sedation.

Precautions for Use. The incidence of adverse reactions with the benzodiazepines is low. Nausea and vomiting, coughing, and hiccoughs have occasionally been noted. Respiratory depression with prolonged somnolence may also occur infrequently with midazolam. These effects have been rapidly and effectively reversed with physostigmine administration and with the specific benzodiazepine antagonist, flumazenil.[49,50]

Caution should also be observed in the management of elderly patients with the benzodiazepines. In general, dosages should be reduced by at least 25%, and there is a

less frequent need for readministration. Cardiac output is diminished in the elderly patient, and the onset of sedation is delayed after the intravenous administration of these drugs. Reduced plasma volume, protein binding, and central nervous system function act to increase the potency of the drugs. Reduced metabolic rate, hepatic and renal clearance, and a higher percentage of body fat tend to slow metabolism and elimination and allow for drug accumulation. This increases the duration of action of the benzodiazepines, and prolongs the interval between readministration.

The benzodiazepines must never be used for intravenous sedation without individualization of dosage. Prior to IV administration of any dose, oxygen and resuscitative equipment for the maintenance of a patent airway and support of ventilation should be readily available. Patients should be continuously monitored for early signs of hypoventilation or apnea. Neither diazepam nor midazolam should be administered by rapid or single bolus intravenous injection. This mode of administration has resulted in serious cardiorespiratory events, predominately in older, chronically ill patients and especially if other cardiorespiratory depressant agents are being taken concomitantly. Midazolam especially has been associated with respiratory depression, apnea, and respiratory and/or cardiac arrest in this age group, sometimes resulting in death. These events have almost always been a consequence of improper midazolam administration as well as violations of the tenets of diligent anesthesia care.

Adverse reactions such as agitation, involuntary movement, hyperactivity, and combativeness have been reported with the benzodiazepines. These reactions may be due to inadequate or excessive doses or improper administration. However, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reaction.

The water solubility and rapid clearance of midazolam make it a clear choice over diazepam for intravenous conscious sedation. Additionally, midazolam produces a more profound and prolonged amnestic effect than diazepam. This effect does not necessarily correlate with the clinical sedation level. Thus, patients are more likely to experience amnesia without having to be heavily sedated. This should serve to enhance the experience of both the patient and the clinician.

Antiemetics. The antiemetics are structurally similar to antipsychotic agents but which happen to have antiemetic effects. They consist of two drug groups, the phenothiazines and the butyrophenones, both of which have similar pharmacologic properties.[51] Promethazine (Phenergan) and prochlorperazine (Compazine) are phenothiazine derivatives, and droperidol (Inapsine) is a butyrophenone.

Additional pharmacological properties of these drugs include ganglionic and alpha-adrenergic blocking effects, anticholinergic activity, anti-dopaminergic effects, and antihistaminic properties. They also potentiate the effects of other central nervous system depressants. Postural hypotension is common when rapidly changing position from supine to upright. Because of the variety of actions, drug interactions are also common with the antiemetics. In combination with epinephrine, the alpha-blocking properties of the phenothiazines could allow the beta effects of epinephrine to predominate. This could result in a precipitous drop in blood pressure.

The anticholinergic effects of the antiemetics can lead to problems either alone or in combination with other anticholinergic drugs such as tricyclic antidepressants, antihistamines, and atropine. A central anticholinergic syndrome characterized by anxiety, agitation, disorientation, restlessness, delirium, or stupor may occur. While rarely life-threatening, it can be extremely disruptive and is to be avoided.

Other potentially disheartening side effects of the antiemetics are extrapyramidal reactions. These are mediated through the dopaminergic blocking effects of the drugs. It is ironic that the same mechanism that produces the desirable effect of emesis control also produces the undesirable effects of extrapyramidal reactions. These are characterized by parkinsonian-like tremors at rest, akathisia (compelling need to be in constant motion), dystonia (facial grimacing and torticollis), and tardive dyskinesia (sucking and smacking of the lips, lateral jaw movements, darting of the tongue).

It should be obvious that due to the potential variety of adverse effects, antiemetic drugs are to be used only as an adjunct to intravenous sedation. The routine prophylactic use of antiemetic agents is not necessary since the incidence of nausea and vomiting associated with conscious sedation is rare. The risks of routine administration far outweigh the perceived benefits, thus relegating these drugs to the role of adjuncts in susceptible individuals.

Antisialogogues. The role of antisialogogues in anesthetic practice probably evolved from the early days of ether anesthesia when excessive airway secretions caused significant management problems. Atropine and scopolamine where used to produce a dry field, reduce the incidence of laryngospasm, and improve visualization of the airway. These drugs are parasympatholytic or vagolytic agents. Among other things, they reduce salivary flow, increase the heart rate, and cross the blood/brain barrier to produce sedation. Scopolamine produces much more sedation than atropine, and is still used as a sedative agent in some techniques. However, it can produce the central anticholinergic syndrome, and therefore

Table 7. Comparative Summary of Intravenous Agents

Drug	*Dose*	*Onset*	*Duration*
Diazepam	0.15–0.3 mg/kg*	0.5–1 min	45 min
Midazolam	0.05–0.075 mg/kg*	1–2 min	30–60 min
Morphine	0.05–0.1 mg/kg	5–10 min	2–4 hr
Meperidine	0.3–0.6 mg/kg	2–4 min	30–45 min
Fentanyl	0.001–0.002 mg/kg	30 sec	30–60 min
Nalbuphine	0.05–0.1 mg/kg	2–3 min	2–4 hr
Butorphanol	0.007–0.014 mg/kg	2–3 min	2–4 hr
Promethazine	12.5–25 mg	2-3 hr	
Prochlorperazine	5–10 mg	2-3 hr	
Droperidol	0.625–1.25 mg	3-6 hr	
Atropine	0.2–0.4 mg	1 min	1–2 hr
Glycopyrrolate	0.1–0.2 mg	1–2 min	2–3 hr

*Usual dose range for conscious sedation, however, these drugs must be titrated to a clinical endpoint on an individual basis.

has no real value in dental sedation. Atropine may also produce the syndrome, but the incidence is less.

Glycopyrrolate (Robinul) is a quaternary amine which cannot cross the blood/brain barrier. Therefore, it does not produce sedation or the central anticholinergic syndrome. Additionally, it is a more prolonged drying agent than atropine, and its cardiac acceleratory effects are less. Because of this, glycopyrrolate should be the antisialogogue of choice.

As with the antiemetics, the antisialogogues are only adjuncts to the sedative technique. Sedation with a benzodiazepine alone or in combination with an opioid will produce sufficient drying in the vast majority of cases. The routine administration of an antisialogogue is not warranted because of the potential for producing tachycardia or central nervous system side effects. If salivation is a problem even after sedation has been administered, glycopyrrolate is the drug of choice. Atropine should be relegated to the emergency drug kit for the treatment of bradycardia associated with hypotension.

A comparative summary of useful drugs for intravenous conscious sedation is provided in Table 7.

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