CHAPTER 25

Pharmacology

As can be seen in Chapter 10, a large number of drugs are available for use intravenously to provide sedation. These drugs encompass a wide range of categories, primarily the sedative-hypnotics, narcotics, and anticholinergics. Those drugs used most frequently in IV sedation are listed in Table 25-1. Also listed in that table are several agents (indicated by an asterisk) that are *not* recommended for IV sedative use by doctors who have not completed at least 1 year of full-time residency in anesthesiology. They will be discussed briefly in this chapter so that the doctor may understand the rationale behind their not being recommended.

BENZODIAZEPINES

The benzodiazepines have become the most commonly used IV sedative agents in dentistry and perhaps also in medicine. Four benzodiazepines will be discussed (Table 25-2), three of which are presently available for use in the United States and one of which is available outside the United States.

Diazepam

Diazepam was synthesized in 1959 by Sternbach and Reeder. The drug became available as Valium (Hoffmann-LaRoche) in 1963 and shortly thereafter became the most prescribed oral medication in the Western world, a position it only recently relinquished to cimetidine (Tagamet). Diazepam is also available in a parenteral preparation for IM (Chapter 10) and IV use.

IV use of diazepam appears to have begun with the work of Davidau in Paris in 1965. This was followed shortly thereafter by a report by Main in 1967, who used diazepam as an adjunct to the Jorgensen technique. In 1968 Brown reported on 40 cases in which diazepam was used alone, the

Table 25-1. Drugs available for IV sedation

Sedative-hypnotics and antianxiety drugs
Benzodiazepines
  Diazepam
  Lorazepam
  Midazolam
  Flunitrazepam
  Chlordiazepoxide*
Barbiturates
  Pentobarbital
  Secobarbital
  Methohexital*
  Thiopental*
  Thiamylal*
Antihistamines
  Promethazine
  Hydroxyzine*
Narcotic agonists
  Meperidine
  Morphine
  Alphaprodine
  Fentanyl
Narcotic agonist/antagonists
  Pentazocine
  Nalbuphine
  Butorphanol
Narcotic antagonist
  Naloxone
Anticholinergics
  Atropine
  Scopolamine
  Glycopyrrolate
Antidotal drugs
  Naloxone
  Nalbuphine
  Physostigmine
  Procaine
Others
  Innovar (droperidol with fentanyl)*
  Ketamine*

*Not recommended for use in IV sedation.

319

Table 25-2. Benzodiazepines for IV administration

Generic name	Proprietary name	Mg/ml	Duration of action (minutes)	Average sedative dose (mg)
Diazepam	Valium	5	45	10-12
Lorazepam	Ativan	2, 4	6-8 hours	2-4
Midazolam	Ro 21-3981/001	5	30	2.5-7.5
Chlordiazepoxide (not recommended)	Librium			

drug being administered until the patient felt sleepy.

In 1969 O'Neill and Verrill reported on the use of IV diazepam for the production of sedation in minor oral surgical procedures, with good to excellent results in 51 of 52 patients treated. The following year O'Neill reported on 55 patients undergoing dental surgical procedures lasting between 20 and 45 minutes. IV diazepam provided successful sedation and cooperation in 49 patients, four others moved and spoke occasionally but were able to be treated, and two patients required additional IV medications (methohexital) for treatment to be completed successfully.

The dosage used in these patients was that required to produce marked ptosis (drooping of the upper eyelid). Halfway ptosis of the upper eyelid is now recognized as the Verrill sign. The practice of administering diazepam until the appearance of the Verrill sign produces a sedative level that is often more profound than necessary and is not reommended for routine use.

Peter Foreman in New Zealand used diazepam in combination with atropine and incremental doses of methohexital. Although successful, he stated that the addition of even small amounts of methohexital greatly increased the risk of overdosage. In his next study Foreman used diazepam alone for a considerable array of dental therapies, finding that although the degree of amnesia produced by diazepam varied significantly from patient to patient, virtually all patients agreed that dental treatment had been at least tolerable rather than an ordeal. He found that IV diazepam had made it possible to treat those patients who may not have received proper treatment in the past because of fear. Foreman stated, "Diazepam has become the drug of choice for the trained general dental practitioner, as well as for the introduction of dental students to intravenous sedation."

Chemistry. Diazepam is a member of the 1,4- benzodiazepine group of compounds. The chemical formula for diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H- 1,4-benzodiazepin- 2-one. It is a pale yellow-white crystalline powder with virtually no odor. It is considerably soluble in chloroform and acetone, moderately soluble in ethanol and ether, and poorly soluble in water.

General pharmacology. It is generally believed today that the emotions are largely controlled by the limbic system, that portion of the brain composed of the amygdala, hippocampus, and septal areas. The midbrain reticular formation, hypothalamus, and thalamus are also involved with the experience, or transmission, of emotions.

Diazepam in very small doses appears to act on the hippocampus, whereas other areas of the brain remain unaffected and the patient remains alert. After oral diazepam administration this action of the drug would be appropriate; however, when administered intravenously a greater effect of diazepam is desired. When administered to the point at which sedation and ataxia (loss of muscular coordination) occur, a more generalized depression of the central nervous system is noted.

More specifically, recent research has suggested that the anxiolytic properties of benzodiazepines are mediated by increased inhibitory nerve transmission. γ-Aminobutyric acid (GABA) is an important inhibitory neurotransmitter in the brain. Glycine (aminoacetic acid), the simplest nonessential α–amino acid, may be the major inhibitory transmitter of the spinal cord. The anticonvulsant and sedative properties of the benzodiazepines may result from a direct agonist effect on stereospecific benzodiazepine receptors, which in turn facilitate the inhibitory action of GABA on its own postsynaptic receptors.

Fate of intravenous diazepam. Diazepam after IV administration achieves a peak blood level in approximately 1 to 2 minutes. The onset of clinical activity is therefore quite rapid. Blood levels of

approximately 1.0 μg/ml may be achieved after an IV dose of 10 to 20 mg of diazepam. Clinically this would normally be equated with a profound level of sedation and a period of amnesia.

As has been mentioned in Chapters 8 and 10, diazepam has a plasma half-life of approximately 30 hours. A very common misconception is that a drug that has a long half-life will possess a long duration of action, whereas one with a short half-life will have a shorter duration of action. This is not true, and diazepam is an excellent example of this. The β–half-life of a drug simply indicates the rate at which the drug undergoes biotransformation in the liver. The factor most responsible for a drug's duration of action is its degree of receptor-site (protein) binding.

Over a period of approximately 45 minutes after the administration of an appropriate dose (for an individual patient) of diazepam, the patient will remain sedated and free of anxiety. In many patients the following three distinct phases of this sedation, each of which lasts approximately 15 minutes, can be observed.

Phase 1: time zero to 15 mintues. During this time the patient is sedated to his maximal degree, since the blood level of diazepam is at its highest level. The patient is still responsive to verbal and physical stimulation, but response time is increased, speech is slurred, and the patient may have difficulty in enunciating words. The patient may not appear to be aware of the presence of the doctor or the assistant during this phase. Amnesia, if it is to occur, will involve procedures occurring at this time.

Phase 2: 16 to 30 minutes. The level of the patient's sedation is somewhat diminished (the patient is more aware than in phase 1; however, he is definitely still sedated, as the diazepam blood level begins to decrease as the drug undergoes redistribution: α–half-life) to those organs and parts of the body that are less rich in vessels than the brain. Response from the patient is more rapid, the slowing down of his responses from phase 1 having diminished or disappeared. Patients can usually recall events occurring during this phase, although in isolated cases amnesia may occur in this phase too.

Phase 3: 31 to 45 minutes. During this time period the typical patient will state that he feels normal again; in other words the feeling of sedation has dissipated. Many doctors are at this time tempted to readminister additional diazepam to the patient; however, this is normally not necessary. Although the patient is indeed no longer feeling sedated, he is also no longer apprehensive. The now falling blood level of diazepam is no longer adequate to maintain the earlier depth of sedation, but it is sufficient to provide an anxiolytic state (similar to the desired actions of oral diazepam). With treatment usually nearing its end and the patient free of pain as a result of administration of local anesthetics, there is no need for readministration of diazepam at this time.

Forty-five to 60 minutes after receiving diazepam, virtually all patients will feel, and in fact look, recovered. This is not a result of the β–half-life of the drug (30 hours) but because of redistribution: α–half-life. The blood level of diazepam at 60 minutes after administration of 20 mg intravenously is 0.25 μg/ml. *The patient is not recovered at this time,* and under no circumstances should the doctor think that this patient is capable of operating a car or leaving the dental office unescorted.

As redistribution of diazepam occurs during this first hour after its IV administration, the level of the drug increases in several storage sites—the fat the wall of the intestines, and the gallbladder. Diazepam stored in fat will usually be retained there since the drug is quite lipid-soluble and the blood supply of fat is relatively poor.

A clinically significant phenomenon can arise at this point, produced by the diazepam now stored in the gallbladder and intestinal walls. Known as the *rebound effect* or *second peak effect,* it involves a recurrence of symptoms of sedation and drowsiness approximately 1 hour after the first meal taken after the patient leaves the dental office. In most cases this will be about 4 to 6 hours after the procedure began. After a meal, especially one rich in lipids, the gallbladder constricts, releasing its contents of bile and unmetabolized diazepam into the small intestine, where over the next hour or so the diazepam is reabsorbed into the cardiovascular system. In some patients the diazepam blood level may reach a point at which clinical signs and symptoms recur. In most cases the patient feels quite tired and wants to lie down for a few minutes. It is absolutely essential, therefore, that the patient receiving diazepam as well as his escort be advised of this possibility prior to discharge from the dental office. The rebound effect is less often observed in patients whose gallbladders have been removed.

Because diazepam is extremely lipophilic, it cannot be excreted through the kidneys and must

therefore undergo biotransformation in the liver.

Biotransformation. Diazepam is biotransformed by one of two pathways. In the first the diazepam molecule undergoes demethylation to desmethyldiazepam, which possesses anxiolytic, but not sedative, effects. Desmethyldiazepam is too lipophilic to permit excretion by the kidney. Desmethyldiazepam has a half-life of 96 hours and eventually undergoes hydroxylation to oxazepam. The second pathway involves the hydroxylation of the diazepam molecule to 3-hydroxydiazepam, another pharmacologically active metabolite also known as temazepam. Temazepam undergoes demethylation into oxazepam.

Oxazepam is yet another water insoluble, anxiolytic benzodiazepine. It is used as an anxiolytic agent by the oral route of administration. The pharmacology of oxazepam (Serax) has been discussed in Chapter 8. The half-life of oxazepam is short, ranging between 3 and 21 hours. It is rapidly biotransformed into its major metabolite, oxazepam glucuronide.

Effects of age and disease. It is frequently stated that drug dosages should be decreased in the very young and the elderly patient as well as in patients with significant liver disease. The clinical properties of diazepam have been well studied in these groups of patents. The following is presented as a summation of that research:

In patients age 2 years and older, diazepam is handled as in an adult. The only significant clinical advice is to adjust the dose of the drug appropriately. With titration by the IV route, clinical results are usually achieved at smaller doses.

In the geriatric patient the dosages of diazepam by the IV (or any other) route should be decreased for several reasons. The rate at which the drug undergoes biotransformation is decreased in patients in this age group. In addition, when administered orally, absorption of the drug from the gastrointestinal tract will be slowed somewhat. However, the most important reason for the apparent *increased sensitivity* of older patients to diazepam and other drugs is related primarily to protein binding. Elderly patients exhibit decreased protein binding of drugs. This means that there will be more of the free, unbound drug available within the blood to cross the blood-brain barrier and produce CNS depression. Diazepam is offered as an example: In the younger patient diazepam is approximately 98.5% protein bound. Therefore, the clinical effects of the diazepam will be produced by only 1.5% of the dosage administered—the non–protein bound diazepam. In the elderly patient, in whom protein binding is not as effective, diazepam may be 97% protein bound, still a significant figure, but one permitting 3% (or twice as much) non–protein bound diazepam to be available to produce CNS depression. It becomes obvious that when administered the same dose of the drug, the clinical actions on the elderly patient will be exaggerated. The dosages of diazepam by the oral and IM routes must be decreased in the elderly patient. With IV administration, titration will provide effective sedation at what will probably be a smaller dose of the drug than is usually given.

Skeletal muscle relaxation. Diazepam, as well as the other benzodiazepines, produces skeletal muscle relaxation. Research has demonstrated that the muscle-relaxant properties of benzodiazepines are caused by central rather than peripheral effects. Monosynaptic reflexes such as the knee jerk reflex are essentially unaffected by even large doses of diazepam, whereas polysynaptic reflexes are depressed by rather small doses.

Anticonvulsant activity. Benzodiazepines have important anticonvulsant properties. Diazepam, chlordiazepoxide, nitrazepam (as well as other benzodiazepines) have the ability to antagonize the convulsive effects of the local anesthetic overdose produced by lidocaine, mepivacaine, bupivacaine, cocaine, and procaine.

In one study the seizure threshold for lidocaine-induced tonic-clonic seizure activity was 8.5 mg/kg. When IM diazepam was administered 60 minutes before treatment in a dose of 0.25 to 0.5 mg/kg, the seizure threshold was elevated to 16.8 mg/kg of lidocaine. Although the barbiturates also provide protection (e.g., pentobarbital, 10.0 mg/kg), they also produce profound behavioral, cardiovascular, and respiratory depression, compared to the minimal effects produced by the benzodiazepines.

In the management of grand mal epilepsy the benzodiazepines have not supplanted phenytoin and phenobarbital as oral maintenance anticonvulsants. IV diazepam is the drug of choice, however, in the management of status epilepticus and acute seizure activity. Once the seizure has been controlled, maintenance therapy with other anticonvulsants is initiated.

Cardiovascular system. Hemodynamic studies show that diazepam produces little effect on the cardiovascular system of healthy human subjects. IV diazepam, in a dose of 0.3 mg/kg, produces no

clinically significant changes in either blood pressure or cardiac output.

Diazepam has been compared with thiopental as a preanesthetic induction agent in the cardiovascularly compromised patient (ASA III and IV). Administered intravenously in a dose of 0.2 mg/kg, fewer than 1% of the patients studied experienced a reduction of cardiac output of more than 15% and none had a mean blood pressure reduction of more than 15%. In contrast, on receiving 2 mg/kg of thiopental, 85% of the patients exhibited more than a 15% reduction in cardiac output, whereas 68% demonstrated more than a 15% reduction in blood pressure.

Adverse hemodynamic effects attributable to the benzodiazepines are rare in humans, even in patients with significant cardiac or pulmonary disease.

Respiratory system. *All sedative-hypnotics, including the benzodiazepines, are potential respiratory depressants.* When studied in patients without pulmonary disease, respiratory depression produced by intravenously administered benzodiazepines is barely detectable. Additionally and quite significantly, the benzodiazepines do *not* potentiate the respiratory-depressant actions of narcotics.

Hepatic disease. Agitation and combativeness are not infrequently encountered among patients with liver disease. Murray-Lyon et al., in a study of patients with severe parenchymal liver disease, administered diazepam intravenously. Adequate sedation was achieved in all patients with no deterioration of their clinical status. Diazepam, when administered with care, is an appropriate sedative agent for patients whose liver function is impaired.

Pain. In general, studies have failed to demonstrate specific analgesic properties of the benzodiazepines; however, high doses of these agents will impair the motor response to painful stimulation. These studies show that benzodiazepines are much more capable of attenuating the emotional response to pain than altering the actual sensation of pain.

Recent studies have demonstrated that diazepam may possess some slight analgesic properties. These properties do not, however, alter the fact that in cases in which pain control is a factor during dental treatment local anesthetics must still be administered in the usual manner.

Amnesia. Intravenously administered diazepam produces what is termed *anterograde amnesia*. This is a lack of recall occurring from the time of injection onward. *Retrograde amnesia*, a lack of recall of events occurring prior to drug administration, is quite rare. Amnesia following diazepam administration is infrequent after IM administration and essentially nonexistent after oral administration.

After IV administration of diazepam the duration of the amnesic phase is approximately 10 minutes; however, considerable variation is noted. During this period patients will respond to stimulation in a normal manner but at a later time (postoperatively or 24 hours later) will be unable to recall the event.

In my experience with IV diazepam sedation, amnesia has developed in approximately 75% of patients. Whereas the length of amnesia has varied, it has been limited in most persons to the first 10 to 15 minutes after diazepam administration. In fewer patients the amnesic effect has lasted through the entire appointment.

The importance of the amnesic phase is that traumatic procedures may be completed at this time with the patient responding normally to them. However, at the termination of the procedure the patient will have no recall of the procedure. The most commonly employed procedure at this time is the administration of local anesthetic. It is quite common for the patient to respond to the initial administration of the local anesthetic (although the procedure should be performed as atraumatically as possible). At the end of the procedure the patient will often question the doctor to find out either how his lip, tongue, etc. became numb without a "shot" or how the drug that was injected into his arm (the diazepam) kept him from feeling the procedure.

Unfortunately the amnesic period will not include the time period prior to the administration of the diazepam; therefore, the patient will almost always remember the venipuncture attempt or attempts.

Although amnesia is usually a welcome benefit of IV sedation, the absence of amnesia does not mean that the procedure was a failure. The goal of sedation is relaxation of the patient so that treatment can be carried out in a more ideal manner. The presence or absence of amnesia should not alter this fact. Lack of recall should be considered the "icing on the cake."

Contraindications. Injectable diazepam is contraindicated in patients with the following:

Known allergy to diazepam or other benzodiazepines

Acute narrow-angle glaucoma and open-angle

glaucoma, unless the patient is receiving appropriate therapy

Warnings. Probably the most significant side effect of intravenously administered diazepam is the occurrence of venous thrombosis, phlebitis, local irritation, or swelling. Although these complications are quite rare when IV diazepam is administered as recommended in Chapter 26, the manufacturer of diazepam, Hoffmann-LaRoche Inc., recommends the following as a means to minimize this possibility:

1. The solution should be injected slowly, taking at least 1 minute for each milliliter (5 mg).
2. Small veins, such as those on the dorsum of the hand or wrist, should not be used.
3. Extreme care should be taken to avoid intraarterial administration or extravasation.
4. Diazepam should not be mixed or diluted with other solutions or drugs in a syringe or infusion flask.
5. If it is not feasible to administer diazepam directly intravenously, it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Other warnings include the following:

6. Extreme care must be exercised when diazepam is administered to elderly or debilitated patients and to those with limited pulmonary reserve because of the possibility of apnea or cardiac arrest or both.
7. Concomitant use of barbiturates, alcohol, or other CNS depressants increases depression with increased risk of apnea.
8. When diazepam is administered with a narcotic analgesic, the dosage of the narcotic should be reduced by at least one-third and should be administered in small increments.

The administration of IV diazepam as recommended in Chapter 26 takes into account these warnings. Titration will prevent accidental overdose in the preceding situations.

Use in pregnancy. Any drug that crosses the blood-brain barrier will also cross the placenta into the fetus. An increased risk of congenital malformation associated with the administration of benzodiazepines during the first trimester of pregnancy has been suggested in several studies. Since the administration of these agents in dentistry is rarely a matter of urgency, their use during this period cannot be recommended. The possibility that a woman of childbearing potential may be pregnant at the time diazepam is used should always be considered.

DIAZEPAM

The medical history of patients receiving diazepam should be checked for the following:

Allergy or hypersensitivity to benzodiazepines

Glaucoma (untreated)

Phlebitis, thrombophlebitis

Pediatric use. Children 2 years of age and older handle diazepam as adults do. The major consideration is the dosage, which in all likelihood will be smaller than that for the typical adult. If administered intravenously, titration will provide the proper safeguard to prevent overdosage.

The administration of IV diazepam to younger children in the dental setting has not always provided ideal sedation. Difficulties exist in establishing the venipuncture in any of these patients. Even more significant, however, is the child's response to the feeling of being sedated. Whereas the adult will become more relaxed and cooperative as the effect of the diazepam intensifies, many younger children will appear to "fight" the effect, becoming increasingly agitated and uncomfortable. Some persons will term this a paradoxical reaction to the drug. It is my feeling that the child is responding to the altered sensations occurring in his head. Being unaccustomed to this feeling, the child tries to move around so as to "get away" from it. Diazepam used alone in younger children does not provide a consistently adequate level of sedation.

Precautions. When combined with other psychotropic agents, careful consideration must be given to possible potentiation of drug effect. Categories such as the phenothiazines, narcotics, barbiturates, monoamine oxidase inhibitors, and other antidepressants are included.

Since metabolites of diazepam are excreted in the kidneys, the administration of diazepam in patients with compromised renal function should be undertaken with care.

Lower dosages may be required for the elderly or debilitated patient.

Patients receiving diazepam intravenously must be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle. Patients should also be advised against the use

```
┌─────────────────────────────────────────────┐
│                                             │
│               DIAZEPAM                      │
│                                             │
│   Proprietary name          Valium          │
│   Classification            Benzodiazepine  │
│   Availability              5 mg/ml         │
│   Average sedative dose     12-15 mg        │
│   Maximal single dose       20 mg           │
│   Maximal total dose        30 mg           │
│                                             │
└─────────────────────────────────────────────┘
```

of alcoholic beverages after the administration of IV diazepam.

As a general rule it is my policy to recommend that patients neither drive their car nor consume alcohol for the remainder of that day at least, and not until the next day if recovery at that time is not complete.

Adverse reactions. The most frequently reported adverse reaction to intravenously administered diazepam is venous thrombosis and phlebitis at the site of injection. This will be discussed in Chapter 27. Other less frequently occurring adverse reactions include:

Hyperactivity

Confusion

Nausea (extremely rare)

Changes in libido

Hiccoughs (not uncommon; more annoying than anything)

Decreased salivation (a benefit in dental treatment)

Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, rage, and stimulation. The general term for this phenomenon is *emergence delirium.* It is seen more frequently with scopolamine administration and will be discussed thoroughly in Chapter 27.

Dosage. The following directions regarding recommended dosage are taken from the diazepam package insert:

Dosage should be individualized for maximal beneficial effect. The usual recommended dose in older children and adults ranges from 2 mg. to 20 mg. IV, depending on the indication and its severity. Lower doses, usually 2 to 5 mg., . . . should be used for elderly or debilitated patients.

The dose of intravenously administered diazepam will always be determined for the individual patient by titrating the agent slowly into a rapidly running IV infusion. In this manner each patient will receive the dose appropriate for sedation, and overdosage should not occur.

Availability. Valium (Hoffmann-LaRoche):5mg/ml in 2 ml ampules, 10 ml multiple-dose vials, and 2 ml preloaded syringe. Injectable diazepam consists of the following ingredients:

40%	Propylene glycol
10%	Ethyl alcohol
5%	Sodium benzoate and benzoic acid as buffers
1.5%	Benzyl alcohol as preservative

Propylene glycol and ethyl alcohol are needed because diazepam is lipid soluble and relatively water insoluble; therefore, it requires a nonaqueous solvent system. Many of the complications and side effects attributed to diazepam, especially phlebitis, are in fact produced by the propylene glycol, which is also a major component of antifreeze.

The IV administration of diazepam can produce a sensation of burning in some patients. This is caused not by the diazepam but rather by the propylene glycol vehicle. It is recommended that the patient be advised of this possibility as the drug is administered. The doctor will tell the patient that there may be a feeling of warmth as the drug is injected. This is entirely normal and will pass within a few minutes. As the drug is carried by the blood away from the injection site this sensation fades away. Its occurrence may be minimized by opening the IV infusion to a rapid rate prior to the injection of the diazepam. Some persons recommend the administration of 1 ml of 1% lidocaine into the IV line immediately prior to the administration of diazepam. The analgesic properties of lidocaine will prevent the burning sensation from occurring. In my experience with diazepam, the slow injection of the drug (diazepam) into the rapidly running infusion will prevent this sensation from arising. Lidocaine administration is not necessary.

The search for a water-soluble benzodiazepine with clinical properties similar to diazepam but without its potential for venous irritation has led to the development of midazolam (see p. 327). Diazepam is presently the most frequently used IV sedative within dentistry. It is a drug that, when used as recommended, is quite safe and extremely effective in the management of severe apprehension and fear of the dental situation. IV diazepam is recognized as one of the two "basic" intravenous sedation techniques in dentistry.

Lorazepam

Lorazepam is a benzodiazepine with antianxiety and sedative effects. It may be administered either intramuscularly or intravenously. Chemically it is 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one. Lorazepam, like diazepam, is virtually insoluble in water. Although available for IV use, lorazepam is seldom used in the ambulatory patient because of the inability to titrate and its prolonged duration of action.

Lorazepam differs from most IV medications in that its onset of clinical action is quite slow. After IV administration lorazepam produces little or no clinical effect for about 5 minutes, with its maximal effect developing approximately 20 minutes after administration. Because of this extremely slow onset of action, lorazepam cannot be titrated to effect. "Average" dosages must be administered—a situation that takes away one of the most important safety features of the IV route of drug administration.

From personal experience with IV lorazepam I have found that it is rather easy to overrsedate the patient. Administration of 1 or 2 mg of lorazepam will usually provide adequate sedation, but because of the bell-shaped curve many patients will be overly sedated at this same dose.

The duration of clinical action of lorazepam is too long for the typical dental procedure. The usual duration of sedative effects of lorazepam is 6 to 8 hours; however, some degree of unsteadiness and sensitivity to the CNS–depressant effects of other medications may persist for as long as 24 hours. I vividly recall the patient who contacted me 36 hours after having received 2 mg of lorazepam intravenously and asked me when the effect of the drug would go away.

The amnesic properties of lorazepam are quite impressive and include both anterograde and retrograde amnesia. Lack of recall is maximal approximately 15 to 20 minutes after IV administration and may include events that occurred throughout the day of treatment. This feeling of "losing a day" may not be very comfortable for the ambulatory patient.

Lorazepam is more highly recommended for use in the hospitalized patient as a preoperative IM or IV medication than in the ambulatory outpatient.

Warnings and precautions. Patients receiving lorazepam must be warned against operating a motor vehicle or machinery or engaging in haz-

---

LORAZEPAM

The medical history of patients receiving lorazepam should be checked for the following:
   Allergy or hypersensitivity to benzodiazepines

---

ardous occupations for 24 to 48 hours after administration of the drug. Dosages of lorazepam should be decreased in patients over the age of 50 years to minimize the risk of oversedation.

The use of scopolamine with lorazepam is not recommended since there is no beneficial effect to be gained; however, additive CNS depression, hallucination, and irrational behavior may be more likely to occur.

Patients must be advised that getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection. Other warnings and precautions for lorazepam are similar to those for diazepam and the other benzodiazepines.

Pediatric use. There are insufficient data to support the use of lorazepam in patients under the age of 18 years.

Adverse reactions. The most frequently noted adverse reactions to lorazepam are caused by a direct extension of its CNS–depressant properties and include the following:

1. Excessive sleepiness that interfered with regional nerve block developed in 6% of patients studied. Patients over the age of 50 years had a significantly greater incidence of excessive sleepiness than did younger patients.
2. Restlessness, confusion, depression, and delirium occurred in 1.3% of patients.
3. Visual and self-limiting hallucinations developed in 1.0% of patients.

Because of its lack of water solubility, lorazepam may produce a burning sensation at the site of the IV infusion during its administration similar to that of diazepam. This occurred in 1.6% of patients receiving the drug. At 24 hours after injection 0.5% still complained of discomfort. Patients should be advised that there may be a slight

```
           LORAZEPAM

Proprietary name          Ativan
Classification            Benzodiazepine
Availability              2 and 4 mg/ml
Average sedative dose     2 mg
Maximal single dose       2 mg
Maximal total dose        4 mg
```

warmth felt at the injection site as the drug is administered and that this is entirely normal and will pass within a few minutes. Slow injection into a rapidly running IV infusion will minimize this reaction.

Dosage. The following directions regarding recommended dosage are taken from the lorazepam package insert:

For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg. total, or 0.02 mg./lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years.

Administration. Lorazepam should be diluted immediately prior to IV administration with an equal volume of a compatible solution. When properly diluted lorazepam may be administered directly into a vein or into the tubing of an existing IV infusion. The rate of injection of lorazepam should not exceed 2.0 mg/minute. Lorazepam may be diluted with the following:
  Sterile water for injection
  Sodium chloride injection
  5% Dextrose injection
Availability. Ativan (Wyeth): 2 and 4 mg/ml in 10 ml vials and 1 ml preloaded syringes. Each milliliter of solution consists of:

2 or 4 mg   Lorazepam
0.18 ml   Polyethylene glycol 400 in propylene glycol
2%   Benzyl alcohol, as a preservative

Lorazepam is not highly recommended for use in dental outpatient sedation because of its prolonged clinical action, its extreme amnesic properties, and primarily the lack of ability of the administrator to titrate the drug to clinical effect.

Lorazepam is an excellent IV sedative for nonambulatory, hospitalized patients for whom close posttreatment monitoring is available for extended periods.

Midazolam

Midazolam is a 1,4-benzodiazepine compound similar in most pharmacological aspects to diazepam. It possesses several attributes that at this time appear to make midazolam somewhat superior to diazepam. As of 1984, midazolam maleate was not available for use in the United States.

Midazolam was synthesized in 1975 by Walser and Fryer at Hoffmann-LaRoche Inc. At this time the drug is known by its research number—RO 21-3981/001. The chemical formula for midazolam is 8-chloro-5(2'fluorophenyl)-1-methyl-4H-imidazo (1,5-a)(1,4) benzodiazepine maleate. It is a colorless crystal in an aqueous solution. Each milliliter contains 5.0 mg midazolam maleate buffered to a pH of 3.3. It is this acidic pH that maintains the benzodiazepine ring in the open configuration required for its water solubility. Once administered, the physiological pH of the body closes the ring, which then provides the chemical structure of the drug required for its efficacy.

It is its water solubility that differentiates midazolam from the other parenteral benzodiazepines—diazepam, lorazepam, and chlordiazepoxide. The requirement for potentially irritating solvents, such as propylene glycol, is eliminated. Water solubility of midazolam is produced by the imidazole substitution at the 1,2 position of the 1,4-benzodiazepine ring structure and because midazolam is the salt of an acid. It is this water solubility that is responsible for the positive findings of lack of burning sensation on injection and the absence of phlebitic sequelae at the injection site.

Pharmacokinetics and biotransformation. Midazolam undergoes metabolism in the liver by hydroxylation into three major metabolites. Whereas the major metabolites of diazepam are pharmacologically active anxiolytics, the major metabolites of midazolam have no pharmacological activity. In addition, because of the lack of active metabolites and its shorter half-life, a rebound effect is not evidenced with midazolam.

The α–half-life (produced by distribution and redistribution) of midazolam has been recorded as 4 to 18 minutes. The β–half-life (the result of metabolism and excretion) is 1.7 to 2.4 hours. By contrast, diazepam's β–half-life is 31.3 hours. The shorter half-lives of midazolam appear to make the drug more ideally suited to ambulatory sedation procedures: a relatively short duration of action combined with a relatively rapidly inactivated and excreted drug.

Midazolam is 94% protein bound, binding occurring primarily in the serum albumin. Midazolam possesses a relatively rapid onset of action, the induction of general anesthesia having ranged from 55 to 143 seconds.

Amnesia. Midazolam, like the other parenteral benzodiazepines, has the ability to produce anterograde amnesia. In a study by Conner et al. (1978), midazolam provided amnesia in the following percentage of patients:

Time after injection (minutes)	Amnesic patients (percentage)
2	96
30	87.5*
32	69
43	57

These results indicate that midazolam is superior to diazepam, lorazepam, or lorazepam and scopolamine in providing anterograde amnesia. Seventy-one percent of the patients in the study by Conner et al. did not recall having been in the recovery room. Some other studies have not demonstrated these same remarkable results, but in all cases the degree of anterograde amnesia provided by midazolam was at least equal to that produced by diazepam. Retrograde amnesia is not produced by midazolam.

Duration of clinical activity. Because of its short α–half-life, the duration of clinical sedation seen with midazolam is somewhat shorter than that of diazepam. Its duration of action is therefore quite compatible with the typical 1-hour dental procedure.

Cardiorespiratory activity. Midazolam, as a typical member of the benzodiazepines, has minimal effect on the cardiovascular and respiratory dynamics of the ASA I or II patient in usual doses. IV doses of 0.15 mg/kg of midazolam in healthy persons have produced statistically significant, but clinically insignificant, decreases in arterial blood pressure and increases in heart rate (Forster et al., 1980). However, other researchers (Brown et al., 1979) noted no untoward cardiovascular response with similar doses. In fact Gath (1981) recommends midazolam as an induction agent for patients with ischemic heart disease because of its rapid onset of action and minimal effects on the cardiovascular system.

---

*From Fragen, R.J., and Caldwell, N.J.: Recovery from midazolam used for short operations, Anesthesiology **153**:511, 1980.

MIDAZOLAM
MIDAZOLAM

The medical history of patients receiving diazepam should be checked for the following:
Allergy or hypersensitivity to benzodiazepines
Acute pulmonary insufficiency
Respiratory depression

Diazepam and midazolam both produce the same effects on the respiratory system. A dose of 0.3 mg/kg of diazepam and 0.15 mg/kg of midazolam produced comparable depression of respiratory response to CO_2 in healthy volunteers (Forster et al., 1980). They concluded that midazolam and diazepam injected intravenously in equipotent doses depress respiration significantly and similarly. The results of their study indicate that this is a result of a direct depression of central respiratory drive rather than being caused by a simultaneous depression of the muscles of respiration, although this cannot be excluded.

In all cases the cardiovascular and respiratory depression noted with midazolam were typical for parenteral benzodiazepines and significantly less than those observed following equipotent doses of barbiturates (thiopental, pentobarbital). No cardiac arrhythmias were provoked by midazolam administration.

Side effects. The most frequently voiced complaint after midazolam administration is dizziness. In the study by Conner et al. (1978), 46% of patients mentioned this. Despite this, 92% stated that they enjoyed the feeling produced by midazolam and 100% said that they would accept the drug again if they required another operation.

Midazolam currently is known as RO 21-3981/001 and is produced by Hoffman LaRoche Laboratories in the United States. In Great Britain midazolam is available for IV use under the trade name Hypnovel (Hoffmann-LaRoche). As currently marketed in Great Britain, midazolam is available in 2 ml ampules containing 5 or 10 mg/ml.

Dosage. Midazolam is approximately 1.5 times as potent as diazepam. The mean effective dose for 50% of subjects (ED_{50}) for the induction of general anesthesia is 0.20 mg/kg, although different studies have determined different values. Reves et al. (1981) determined the following:

```
┌─────────────────────────────────────────┐
│                                         │
│              MIDAZOLAM                   │
│                                         │
│  Proprietary      RO 21-3981/001 (United │
│    name             States)             │
│                   Hypnovel (Great Britain)│
│  Classification   Benzodiazepine         │
│  Availability     5 mg/ml                │
│  Average sedative 2.5-7.5 mg             │
│    dose                                  │
│  Maximal single   Not available          │
│    dose                                  │
│  Maximal total    Not available          │
│    dose                                  │
│                                         │
└─────────────────────────────────────────┘
```

ED_{50}　0.13 mg/kg
ED_{95}　0.20 mg/kg
ED_{99}　0.23 mg/kg
ED_{100} > 0.23 mg/kg

Clinically adequate sedation may be provided with an IV dose of 0.09 to 0.12 mg/kg. For the typical 70-kg (154-pound) patient this is equal to doses of 6.3 and 8.4 mg, respectively. Young (1983), reporting on 100 cases of midazolam sedation in dentistry in patients ranging in age from 10 to 70 years, achieved adequate sedative effects with a dosage range of 2.5 to 7.5 mg of midazolam. The manufacturer recommends, "as a guide, 0.07 mg/kg. body weight. . . Total dose varies between 2.5 and 7.5 mg., but on occasion, more may be necessary. In elderly patients a dose of 2.5 mg. may be adequate."

Availability. As mentioned previously, midazolam is still a research drug and as such is not yet generally available. At what point it will be released for use in the United States is not known at the present time.

Midazolam maleate appears to be a highly effective antianxiety agent, useful by both IM and IV routes of administration. The following is a comparison of midazolam and diazepam:

	Midazolam
Potency	1.5 times that of diazepam
Onset	More rapid than diazepam
Duration of action	Slightly shorter than diazepam
Redistribution	More rapid than diazepam
Metabolism and excretion	Significantly more rapid than diazepam
Active metabolites	None known to date
Amnesia	Anterograde, not retrograde
Duration of amnesia	Longer than diazepam
Respiratory effects	Equal to diazepam in equipotent doses
Cardiovascular effects	Equal to diazepam in equipotent doses
Complications	Injection site complications (phlebitis) insignificant
Ability to dilute drug	Water soluble; can be diluted

As with all other CNS depressants, the dose of midazolam must be decreased when other CNS depressants are being administered concomitantly. In addition after IV sedation the patient must be escorted from the dental office with a responsible adult companion and be advised not to have any alcoholic beverages and not to engage in any hazardous occupation requiring complete mental alertness, such as operating machinery or driving a motor vehicle, for approximately 24 hours.

Flunitrazepam

Flunitrazepam is a water-soluble benzodiazepine derivative that is chemically and pharmacologically related to diazepam and other drugs of this group. The chemical formula for flunitrazepam is 5-(o-fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2H-1,4-benzodiazepin-2-one. The sedative, antianxiety, amnesic, and muscle-relaxing properties of flunitrazepam are similar to those of diazepam except that its sedative and sleep-inducing properties are more pronounced and long-lasting than those of diazepam. Foreman (1982) has reported that flunitrazepam appears to be approximately 15 times as potent as diazepam and must therefore be diluted prior to administration to assure precise titration.

Flunitrazepam is available in a 1 ml ampule containing 2 mg of the agent. The manufacturer suggests diluting the drug with 1 ml of sterile water for injection prior to use, providing a solution of 1 mg/ml. Foreman, however, suggests that further dilution is warranted, recommending the dilution of 2 mg of flunitrazepam in 9 ml of sterile water, providing a solution of 0.2 mg/ml.

After IV administration for the induction of general anesthesia, flunitrazepam produced its clinical effects within 1 to 3 minutes, with the peak effect being reached in 5 minutes. The duration of the effect ranged from 10 to 60 minutes, with significant variation with dosage (1 to 6 mg). The $\alpha-$ and $\beta-$half-lives of flunitrazepam are 19 and 34 hours.

Side effects and complications associated with flunitrazepam administration are similar to those

previously discussed for the benzodiazepines. As with most benzodiazepines, flunitrazepam is remarkably free of respiratory- or cardiovascular-depressant effects. The most frequently reported side effects associated with flunitrazepam administration are diaphoresis, ataxia, erythema, blurred vision, hypersalivation, dry mouth, weakness, hypothermia, hypoventilation, and prolonged drowsiness.

The dosage of flunitrazepam should be decreased in elderly and debilitated patients.

The use of alcohol and driving should be prohibited for 24 hours after the administration of flunitrazepam.

Flunitrazepam sedation in dentistry. Foreman (1982) reported on 10 patients to whom flunitrazepam was administered intravenously for sedation. The dosages ranged from 1.4 to 2.0 mg. Treatment conditions ranged from good to excellent in eight of the ten patients. No patient recalled receiving a local anesthetic during treatment (although they all did receive local anesthetics), nor in fact did they recall the dental treatment. They did remember being escorted to the recovery area and being driven home after discharge from the office.

The duration of sedation provided by flunitrazepam is somewhat longer than that produced by diazepam. This would contraindicate its use in shorter procedures (those lasting less than 1 hour) but would be an indication for its administration in longer procedures. Recovery from sedation was less complete than that seen with diazepam, even at 24 hours. In cases in which patient recovery is important, flunitrazepam may not be the desired drug for IV sedation.

Availability. Rohypnol (Hoffmann-LaRoche): 2 mg in 1 ml ampules. Flunitrazepam is not available in the United States at the present time. It is available in both an oral and parenteral form in Great Britain and other countries under the proprietary name Rohypnol.

Chlordiazepoxide

Chlordiazepoxide is also available for injectable use; however, because of the more ready accessibility to the other benzodiazepines, this agent is rarely used parenterally, especially intravenously.

Chlordiazepoxide for IV and IM use must be prepared immediately prior to its administration by mixing a 5 ml dry-filled ampule containing 100 mg of chlordiazepoxide with 5 ml of either sterile physiological saline or sterile water for injection. This produces a concentration of chlordiazepoxide of 20 mg/ml, which is then injected at a rate of 1 ml/minute.

In view of the current availability of diazepam and midazolam, there appears to be little reason for considering the IV administration of chlordiazepoxide.

Summary

The benzodiazepines represent the most nearly ideal agents for IV sedation in the ambulatory patient. Pharmacologically they have little significant effect on the cardiovascular and respiratory systems when administered in recommended doses and utilizing recommended techniques. Diazepam and midazolam are the drugs of choice for IV procedures with a duration of less than 60 minutes. Midazolam appears to possess several significant advantages over diazepam, most important of which are its lack of irritation to vessels and the lack of a rebound or second peak effect.

BARBITURATES

The barbiturates have served as an important group of sedative drugs within dentistry for almost 40 years. Niels B. Jorgensen, the Father of Intravenous Sedation in Dentistry, utilized a barbiturate in his technique of IV premedication, now known worldwide as the Jorgensen technique.

Although several barbiturates are available for sedation by the IV route (Table 25-3), only one—pentobarbital—has retained any popularity. Secobartibal is used intravenously in the Berns technique. Other barbiturates used intravenously include the ultrashort–acting general anesthesia induction agents—methohexital, thiopental, and thiamylal.

Pentobarbital sodium

Chemically pentobarbital sodium is sodium 5-ethyl-5-(1-methylbutyl) barbiturate. The sodium salt is freely soluble in water and alcohol. Pentobarbital is classified as a short-acting barbiturate. It possesses characteristics of the entire group of barbiturates, which will now be discussed.

Pharmacology. Barbiturates are frequently classified according to their duration of clinical action following oral administration (see Table 8-5). After oral and IV administration, the clinical actions of pentobarbital will be observed for approximately 2 to 4 hours.

Table 25-3. Barbiturates for intravenous administration

Generic name	*Proprietary name*	*Amount mg/ml*	*Duration of action*	*Average sedative dose (mg)*
Pentobarbital	Nembutal	50	2-4 hours	125-175
Secobarbital	Seconal	50	2-4 hours	100-150
Methohexital	Brevital (United States)			
	Brietal (Great Britain)	10	5-7 minutes	*
Thiopental	Pentothal	25	—	*
Thiamylal	Surital	25	—	*

*Not recommended for IV sedation.

All of the barbiturate sedative-hypnotics are generalized depressants, with the central nervous system being the most sensitive system. Barbiturates produce a characteristic pattern of CNS depression: the cerebral cortex and the reticular activating system (RAS) are most sensitive to the actions of the barbiturates; the cerebellar, vestibular, and spinal systems less so, and the medulla least sensitive of all.

The RAS is important in the maintenance of a conscious alert state. Sedative doses of barbiturates act on this system to depress ascending neuronal conduction to the cerebral cortex; as a result consciousness is diminished or lost.

Unlike true analgesic drugs, such as the narcotics or salicylates, barbiturates have no effect on the pain threshold except in doses that affect the level of consciousness (as in IV sedation). In the presence of severe pain it is found that barbiturates often make the patient restless and more difficult to manage. This is because of a decreased control over emotions by the cortical centers of the brain. In other words, the patient becomes less inhibited and more likely to respond to a noxious stimulus as a child would. Barbiturates should not be used as the sole agent for sedation when a painful procedure is planned. Analgesics, such as meperidine and local anesthetics, are frequently used when IV barbiturates are administered in order to counteract this negative effect.

The parenteral barbiturates are effective as anticonvulsants and are used in the management of seizures produced by tetanus, epilepsy, and overdose of local anesthetics. However, with the advent of the benzodiazepines, which are equally effective anticonvulsants with a decreased potential for respiratory depression, the use of barbiturates as anticonvulsants has declined.

Respiratory system. The barbiturates produce respiratory depression by a direct action on the medullary respiratory center. The degree of respiratory depression is dose related. Respiratory arrest (failure) is the usual cause of death from barbiturate overdose. As respiratory depression develops from barbiturate administration, the rate of respiration increases while the tidal volume decreases. Respiratory reflexes, such as coughing, sneezing, hiccoughing, and laryngospasm, are only slightly depressed until the degree of CNS depression is pronounced. Laryngospasm is one of the chief respiratory complications of IV barbiturate general anesthesia (see Chapter 31).

Cardiovascular system. In comparison to the respiratory system, the cardiovascular system is quite resistant to the depressant effects of the barbiturates. Normal hypnotic doses are associated with only a slight fall in heart rate and blood pressure, similar to that seen in normal sleep. IV thiopental anesthesia will produce more significant depression of the cardiovascular system. The slight drop in blood pressure observed with IV barbiturate sedation/anesthesia is a result of depression of the vasomotor center with consequent peripheral vasodilation. Larger doses of the barbiturates act directly on smaller blood vessels to produce dilation and increased capillary permeability.

Absorption, metabolism, and excretion. The parenteral barbiturates are highly lipid soluble, a property that facilitates their rapid redistribution from the blood to other tissues within the body. When administered intravenously, the ultrashort-acting barbiturates reach peak concentration in the brain within 30 seconds. During this time the other so-called vessel-rich tissues—heart, liver, and kidneys—also reach saturation levels. Lipid solubility and plasma protein binding of the barbiturates vary (Table 25-4) and are responsible for onset of action and duration of action.

Agents with greater lipid solubility (greater par-

Table 25-4. Characteristics of intravenous barbiturates

Drug	Partition coefficient	Plasma protein binding	Delay in onset of action (minutes)
Barbital	1	0.05	22
Phenobarbital	3	0.20	12
Pentobarbital	39	0.35	0.1
Secobarbital	52	0.44	0.1
Thiopental	580	0.65	Less than 0.1

Modified from Goodman, L.S., and Gilman, A.: The pharmacological basis of therapeutics, ed. 5, New York, 1975, Macmillan Publishing Co., Inc.

Table 25-5. Method of elimination of barbiturates

Primarily excreted by kidney
  Barbital
  Phenobarbital
Degraded by liver and excreted by kidney
  Aprobarbital
Primarily metabolized by liver
  Amobarbital
  Pentobarbital
  Secobarbital
Distributed to body fat, eventually dependent on liver and kidney
  Thiopental
  Thiamylal

Table 25-6. β—Half-lives of selected barbiturates

Drug	β—half-life (hours)
Hexobarbital	4.35
Amobarbital	21.1
Pentobarbital	21.8
Secobarbital	28.9
Phenobarbital	86

PENTOBARBITAL

The medical history of patients receiving pentobarbital should be checked for the following:
  Allergy or hypersensitivity to barbiturates
  Porphyria
  Liver disease
  Asthma
  Respiratory depression
  Alcoholism

---

tition coefficient) have a more rapid onset of action, whereas protein binding relates to the relative duration of action of the agent.

The barbiturates rapidly diffuse out of the blood and are redistributed to all tissues. This leads to a rapid decrease in the blood level of the drug and a termination of clinical activity (α–half-life). The liver and muscles account for most of the volume of barbiturate that is withdrawn from the blood. Body fat, with a poor blood supply, requires approximately 1½ to 2 hours to become saturated. When equilibrium between the barbiturate in the tissues and the blood occurs, the decline in barbiturate blood level is slowed and becomes a measure of the rate of metabolism of the drug.

It is this rapid removal (redistribution) from the blood that accounts for the brief action of the so-called *ultrashort-acting barbiturates,* not their rapid metabolism. Thiopental, for example, undergoes metabolism at the rate of 15% per hour. This important aspect of barbiturate pharmacology will be discussed more fully in Chapter 31.

Barbiturates are eliminated in one of two methods: biotransformation in the liver and excretion through the kidneys. A few barbiturates are largely excreted, others are almost completely inactivated by the liver, and still others are partially excreted and partially metabolized (Table 25-5).

It must be noted that the liver is the most important organ for the metabolism of the barbiturates, although other organs such as the kidneys, brain, and muscle are also involved. Any type of liver disease or dysfunction may tend to prolong the action or intensify the depth of depression produced by the barbiturate and must be considered a relative or absolute contraindication.

The β–half-lives (the time required for biotransformation and excretion) of some of the barbiturates are listed in Table 25-6.

The slow release of these drugs from these tissue depots may be somewhat responsible for the

---

PENTOBARBITAL

Proprietary name	Nembutal
Classification	Barbiturate
Availability	50 mg/ml
Average sedative dose	125-175 mg
Maximal single dose	300 mg
Maximal total dose	500 mg

hangover effects so often noted after barbiturate administration. The day after the administration of IV pentobarbital, some patients will still exhibit clnical signs of CNS depression.

Unwanted effects. The most commonly observed unwanted effects from barbiturate administration are hangover and excitement. Hangover, or unwanted posttreatment lethargy, is produced by the slow reabsorption of the barbiturate from tissue depots into the blood and is more likely to develop with the longer-acting barbiturates.

In some patients the barbiturates will produce excitation rather than depression and the patient will appear to be inebriated, becoming quite talkative. This is an idiosyncratic response and is more likely to be seen after administration of phenobarbital, although it may develop with other barbiturates.

Patients with a personal or familial history of *acute intermittent porphyria* represent one of the few absolute contraindications to barbiturate administration. (See Chapter 5 for a discussion of acute intermittent porphyria.)

Allergy to barbiturates, although uncommon, is more likely to develop in patients with histories of allergy, urticaria, and angioedema. Barbiturate use, especially chronic, can produce drug dependence and tolerance. In addition drug-drug interactions with other CNS depressants must be considered whenever concomitant drug therapy is used.

Warnings. Patients receiving pentobarbital must be advised against performing any potentially hazardous tasks such as driving a vehicle or operating machinery. In my clinical experience patients who have received pentobarbital do not want to do anything other than return home and go to sleep in the immediate period after sedation. They are advised that the next day they will probably be fully capable of functioning normally; however, in some few instances signs and symptoms may persist and the patient is advised to continue resting.

The use of alcohol or other CNS depressant medications after pentobarbital administration must be cautioned against since potentially significant additive effects may develop. Prescriptions for postoperative analgesics must take this into consideration. The use of a long–acting local anesthetic, such as bupivacaine or etidocaine, is recommended. Chronic use of barbiturates will induce liver microsomal enzyme activity and may influence the dosage of pentobarbital required for sedation. Because pentobarbital crosses the placenta, its use is contraindicated during pregnancy.

Precautions. Pentobarbital should be used with caution in patients with impaired liver function or a history of drug dependence or abuse. A history of cirrhosis or recent hepatitis represents a relative contraindication to pentobarbital administration, as does recent or chronic alcoholism. The alcoholic person may respond in one of three different ways to administration of the barbiturate: In most instances the response will approximate the usual response with doses within the normal range. In the second possible response the alcoholic patient's liver will have produced a greater volume of hepatic microsomal enzymes, which will decrease the patient's response to the usual dosage. Significantly larger doses may be required to provide a sedative effect with pentobarbital in this patient. This response will usually be seen in the "early" alcoholic, prior to the development of liver dysfunction—fatty degeneration (cirrhosis)—has occurred, making the patient less able to manage the usual dose of barbiturates. In this situation the patient will overrespond to usual dosages of pentobarbital and other barbiturates.

Patients with any respiratory disorder but especially *asthma* should be administered pentobarbital with caution. Since the barbiturates are potent respiratory depressants, they should be administered carefully in all patients with a suspicion of pulmonary dysfunction.

The parenteral solution of pentobarbital is quite alkaline (pH of 9.5). Extravascular injection of the drug may produce tissue irritation and possible damage, such as sloughing or sterile abscess formation (see Chapter 27).

Hypotension may develop following the rapid IV administration of pentobarbital. When the agent is administered at the recommended rate of 1 ml/minute, such a response is unlikely to develop.

Patients must be warned against operating a motor vehicle for the remainder of the day that the drug is administered. As mentioned previously, most patients receiving pentobarbital have no desire to drive a car.

Adverse reactions. Possible adverse reactions to pentobarital administration include the following:

Respiratory depression
Apnea
Circulatory collapse
Pain
Skin rash
Allergic reaction

Residual sedation (hangover)
Nausea and vomiting
Paradoxical excitement

Coughing, hiccoughing, laryngospasm, and chest-wall spasm have been observed after the IV administration of pentobarbital. Slow administration of the agent minimizes the occurrence of these effects. With over 1000 administrations of pentobarbital (at the USC School of Dentistry), laryngospasm and chest-wall spasm have never been encountered. Bronchospasm may occur, particularly in patients who have a history of bronchial asthma. This represents a relative contraindication to pentobarbital administration. Thrombophlebitis may also develop at the site of drug administration, although the incidence of this complication from pentobarbital is quite insignificant.

Dosage. When administered intravenously, pentobarbital must be titrated to effect. As used in the Jorgensen technique, pentobarbital will be used to provide the suitable level of sedation. The dosage range observed with pentobarbital is quite wide—as little as 30 mg to as much as 300 mg providing the same clinical signs and symptoms in different patients. This wide range of safety with pentobarbital is one of the reasons that this drug may be used in IV sedative procedures. Other barbiturates do not possess this same flat dose-response curve and are therefore not recommended for sedative use by the doctor who is not trained in general anesthesia and management of the unconscious patient.

Although doses of pentobarbital as high as 500 mg have been used to achieve sedation in some patients, it is my recommendation that 300 mg not be exceeded in one dose. Repeat titrations (if needed) should bring the dose up to a maximum of 500 mg for one appointment. The average dose of pentobarbital usually required for adequate sedation in the Jorgensen technique is 125 to 175 mg.

Availability. Nembutal (Abbott): 50 mg/ml in 2 ml ampules and 20 and 50 ml multidose vials. Each milliliter of pentobarbital sodium contains:

50 mg Pentobarbital sodium
40% Propylene glycol
10% Alcohol
Water for injection
pH adjusted to 9.5 with hydrochloric acid and/
  or sodium hydroxide
Air in container displaced by N_2

> ### *SECOBARBITAL*
>
> The medical history of patients receiving secobarbital should be checked for the following:
>   Allergy or hypersensitivity to barbiturates
>   Porphyria
>   Liver disease
>   Asthma
>   Respiratory depression
>   Alcoholism

> ### *SECOBARBITAL SODIUM*
>
> | | |
> |---|---|
> | Proprietary name | Seconal |
> | Classification | Barbiturate |
> | Availability | 50 mg/ml |
> | Average sedative dose | 50-150 mg |
> | Maximal single dose | 150 mg |
> | Maximal total dose | 250 mg |

Secobarbital

Secobarbital is a short-acting barbiturate, similar in action to pentobarbital, that is used intravenously in the Berns technique, a combination of secobarbital with a narcotic and ultrashort-acting barbiturate. The basic pharmacology, warnings, precautions, and side effects of secobarbital are similar to those for pentobarbital.

Dosage. In the Berns technique, when used in combination with other drugs, the maximal recommended dose of secobarbital is 50 mg. When used as the sole agent for sedation, doses of 100 to 150 mg may be used, injected slowly.

Availability. Seconal (Lilly): 50 mg/ml in 1, 2, 10, 20, and 30 ml vials. Secobarbital sodium is available as a powder that is diluted with sterile water for injection. Bacteriostatic water and Ringer's lactate solutions are incompatible with secobarbital sodium. As a powder it comes in ampules containing 250 mg of the drug. It is diluted with 5 ml of diluent to produce a concentration of 5%, or 50 mg/ml. It is also available generically.

Methohexital sodium

Methohexital sodium is an ultrashort-acting barbiturate most frequently used for the rapid induction of general anesthesia (stage 3) or the pro-

---

METHOHEXITAL

The medical history of patients receiving diazepam should be checked for the following:
Allergy or hypersensitivity to barbiturates
Porphyria
Liver disease
Asthma
Respiratory depression
Alcoholism

METHOHEXITAL SODIUM

Proprietary name	Brevital (United States) Brietal (Great Britain)
Classification	Barbiturate
Availability	10 mg/ml
Average sedative dose	10- to 20-mg increments
Maximal single dose	20 mg
Maximal total dose	Approximately 100 mg*

*Procedure should not require more than 20 minutes to complete.

---

duction of short–duration ultralight general anesthesia as frequently used for oral surgical procedures. Methohexital was synthesized by Stoelting in 1957 and was popularized as an agent for outpatient dental anesthesia by Adrian Hubbell in the early 1960s.

Although primarily used as a general anesthetic, methohexital sodium may be used in smaller doses as a sedative-hypnotic agent. Several IV sedation techniques have been developed in which methohexital is used—intermittent methohexital sedation, the Berns technique (secobarbital, meperidine, and methohexital), the Shane technique (hydroxyzine, alphaprodine, and methohexital), and diazepam and methohexital sedation. Although these techniques will be discussed in the following chapter, *the use of methohexital by any person not trained in general anesthesia and in the management of the airway of the unconscious patient cannot be recommended.*

The chemical formula for methohexital sodium is: sodium-a-dl-1-methyl-5-ally1-5-(1-methyl-2-pentyl) barbiturate. It differs from other barbiturate anesthetics in that it does not contain any sulfur. When compared to the actions of other IV barbiturate anesthetics (thiopental, thiamylal), methohexital possesses several advantages:
Shorter duration of action
Faster clinical recovery
Relative absence of local complications
Amnesia
Relatively stable solution

The usual duration of action of a dose of methohexital is 4 to 7 minutes. It is therefore suitable for short procedures requiring less than 20 minutes. Foreman (1982) recommends its use as a sedative only for restorative and minor oral surgical procedures of short duration and says that if this limitation is observed and if the patency of the airway is ensured at all times by effective mouth packing, intermittent methohexital sedation is a safe and useful technique. Because of the steeper dose-response curve of methohexital, it is possible to produce overly deep sedation or light general anesthesia quite accidentally. This relative lack of safety with methohexital is the basis for my recommendation against its use as a sedative by persons without advanced training in general anesthesia and the management of the airway of the unconscious patient. Methohexital is always used as a 1% (10 mg/ml) solution. Contraindications and warnings for methohexital are similar to those for pentobarbital (p. 333).

Adverse reactions. The following are the major adverse reactions observed after the administration of methohexital sodium:
Circulatory depression—most often seen after overly rapid administration of larger doses (greater than 10 to 20 mg)
Thrombophlebitis—not a significant problem
Respiratory depression, apnea—probably the most significant adverse responses to use of methohexital sodium; they are usually dose related; however, in sensitive individuals respiratory depression or apnea may develop at unusually small doses
Laryngospasm—a serious complication that will develop as the patient becomes more deeply sedated if the pharynx contains fluid or foreign matter

Bronchospasm—much more likely to develop in the patient with a history of asthma

Hiccoughs—associated with rapid administration

Skeletal muscle hyperactivity—not uncommon as the patient enters stage 2 of anesthesia; this should not develop with the small doses (10 to 20 mg) recommended for sedation

Emergence delirium

Nausea and vomiting

Acute, life–threatening allergic reactions, although rare, have developed after administration of methohexital sodium

Dosage. When methohexital sodium is used as a sedative in dentistry, it must always be titrated in extremely small doses not exceeding 10 mg. On rare occasion a 20-mg dose may be used by the experienced individual, but this is never to be exceeded.

Since dental procedures in which methohexital sodium is used for sedation should not exceed 20 minutes, the maximal dose of methohexital recommended is 100 mg. In procedures expected to require more than 20 minutes, other IV medications should be used.

In both the Berns and Shane techniques, 10- to 20-mg increments of methohexital sodium are administered after the injection of other IV drugs.

Availability. Brevital (Lilly), Brietal: 500 mg in 50 ml vials. Methohexital is prepared prior to use by adding 50 ml of suitable diluent to the vial to produce a 1%, or 10 mg/ml, solution. Suitable diluents include sterile water for injection, in which case the solution may be stored for up to 6 weeks, and 5% dextrose in water or isotonic (0.9%) sodium chloride solution, in which case the solution is only stable for 24 hours. Each vial of methohexital sodium contains:

500 mg Methohexital sodium
30 mg Anhydrous sodium carbonate

It contains no preservative.

Thiopental and thiamylal

Two other ultrashort-acting barbiturates—thiopental and thiamylal—are available for IV administration. Thiopental (Pentothal, which is manufactured by Abbott) and thiamylal (Surital, manufactured by Parke-Davis) are used for the induction of general anesthesia (stage 3) and as the sole agents for general anesthesia in surgical procedures requiring 30 minutes or less. Thiopental was introduced into clinical practice by Lundy in 1934, whereas thiamylal was first described in 1935 by Volwiler and Tabern. Thiopental is the most widely used ultrashort-acting barbiturate in current hospital practice. The duration of action of both thiopental and thiamylal is longer than that of methohexital. These agents are rarely used in sedative procedures and cannot be recommended for use in this regard. They will be discussed further in Chapter 31.

Summary

Although a number of barbiturates are available for IV administration, there are some important reasons for not recommending some of them for use as IV sedatives. The potent respiratory-depressant properties of this group of drugs, combined with the steep dose-response curves of methohexital, thiopental, and thiamylal, are reason enough to recommend against their use by any doctor not trained in general anesthesia and in management of the airway of the unconscious patient. It is simply too easy to get into trouble with these drugs. There are, however, two barbiturates—pentobarbital and secobarbital—that are recommended for use as IV sedatives. Although pharmacologically similar, pentobarbital is the most commonly used. Possessing a relatively flat dose-response curve, pentobarbital is an excellent agent for sedative procedures requiring 2 to 4 hours.

ANTIHISTAMINES

Two drugs that are classified as antihistamines—promethazine and hydroxyzine—have been used occasionally as IV sedatives. The basic pharmacology of these two drugs has already been discussed in Chapters 8 and 10. In this section only those aspects of their pharmacology relevant to IV administration will be reviewed.

Promethazine

Promethazine is a phenothiazine derivative that is frequently used in dentistry, primarily pediatric dentistry, as a sedative-hypnotic administered either orally or intramuscularly. Promethazine may also be administered intravenously either as a sole agent or in combination with a narcotic.

The clinical duration of action of promethazine after IV administration is approximately 1 to 2 hours. Clinical recovery of the patient at this time is somewhat greater than that observed after pentobarbital administration; however, it is significantly less than that seen with diazepam. Promethazine fills the void between the diazepam/

PROMETHAZINE

The medical history of patients receiving promethazine should be checked for the following:

Allergy or hypersensitivity to promethazine
Glaucoma
Prostatic hypertrophy
Stenosing peptic ulcer
Bladder neck obstruction

PROMETHAZINE

Proprietary name	Phenergan
Classification	Antihistamine
Availability	25 mg/ml
Average sedative dose	25-35 mg
Maximal single dose	50 mg
Maximal total dose	75 mg

---

midazolam sedative actions of less than 1 hour and the 2- to 4-hour sedation provided by pentobarbital.

The most significant adverse reaction to administration of promethazine is the occurrence of extrapyramidal reactions. Clinical signs and symptoms and their management have been discussed in Chapter 8.

Dosage. When used intravenously the usual dose of promethazine required for sedation is approximately 25 to 35 mg. This agent should be used in a concentration of 25 mg/ml. Promethazine may be administered intravenously to children. The drug should be titrated to clinical effect. In most cases the dose will not exceed that for the average adult.

Availability. Phenergan (Wyeth), Fellozine (O'Neal, Jones & Feldman), Lemprometh (Lemmon), Provigan (Reid-Provident), and Zipan (Savage): 25 mg/ml in 1 ml ampules and 10 ml vials. It is also available in a 50 mg/ml concentration that is recommended for IM use only.

Hydroxyzine

Hydroxyzine is an antihistaminic drug that has potent sedative properties, although not as potent as those of promethazine. The chemical formula for hydroxyzine is 1-(p-chlorobenzhydryl)4-(2-[2-hydroxyethoxy]ethyl) piperazine hydrochloride. The pharmacology of hydroxyzine has previously been discussed in Chapters 8 and 10.

Clinically important properties of hydroxyzine include its antiemetic actions and its ability to potentiate the actions of other CNS depressants, such as narcotics and barbiturates.

Hydroxyzine has been recommended for IV use in the Shane technique, which involves the administration of hydroxyzine, alphaprodine, and methohexital. In spite of the success of this technique, there are limitations to its use, not the least of which is the fact that hydroxyzine is not recommended, by its manufacturer, for IV use.

The drug package insert accompanying hydroxyzine states the following under the section on contraindications:

Hydroxyzine hydrochloride intramuscular solution is intended only for intramuscular administration and should not, under any circumstances, be injected subcutaneously, intraarterially, or intravenously.

Hydroxyzine appears to be quite irritating to blood vessel walls, producing an unacceptably high rate of local complications ranging from mild phlebitis to more serious thrombosis. Because of the availability of other equally effective agents that do not produce the same degree of complications and adverse effects, the administration of hydroxyzine intravenously cannot at this time be recommended.

Summary

Promethazine is an effective IV sedative agent. Its primary indication is for IV procedures requiring more than 1, but less than 2, hours.

Hydroxyzine, although an effective sedative, is associated with an unacceptably high rate of localized complications and is not recommended for use intravenously.

NARCOTIC ANALGESICS

The narcotics are used primarily for their analgesic properties. They are excellent drugs for the relief of moderate to severe pain. Although they affect many systems throughout the body, their primary therapeutic actions derive from their effects on the central nervous system. Narcotics are able to produce analgesia, drowsiness, changes in mood, and mental clouding. Of significance is the fact that analgesia is produced without the loss of consciousness. The use of these drugs by the oral

and IM routes has been discussed in Chapters 8 and 10, and the relevant pharmacology has been reviewed in Chapter 10. In this section the potential use of these drugs for IV sedation will be discussed.

The narcotic analgesics may be divided into the following specific categories: (1) narcotic agonists, (2) narcotic agonist/antagonists, and (3) narcotic antagonists. Narcotic agonists are those agents that interact with an opioid receptor and produce physiological change. A narcotic antagonist is a drug that occupies a receptor site with no resultant pharmacological effect. With the appearance in the 1960s of agents such as pentazocine, which had both agonist and antagonist properties, it became necessary to formuate a concept of multiple-opioid receptors in the central nervous system.

Martin et al. (1976) proposed a theory of multiple receptors rather than a single target for opiate agonists. They proposed at least three separate opioid receptors—mu (μ), kappa (κ), and sigma (σ). Table 25-7 lists the various opioid receptors as well as agonist, antagonist, and partial agonist drugs for each. Partial agonists are drugs with properties of both agonists and antagonists. Table 25-8 lists the various physiological responses attributed to the various opioid receptors.

NARCOTIC AGONISTS

Four narcotic agonists—meperidine, morphine, alphaprodine, and fentanyl—are used for the production of sedation in dentistry.

Table 25-7. Opioid drugs and opioid receptors

Receptor	Agonist	Antagonist	Partial agonist
Mu (μ)	Morphine Enkephalins Fentanyl	Naloxone	Butorphanol Nalbuphine
Kappa (κ)	Morphine Fentanyl Ketocyclazocine Butorphanol Nalbuphine	Naloxone	
Sigma (σ)	Pentazocine	Naloxone	Butorphanol Fentanyl
Delta (δ)	Enkephalins	Naloxone	

From Pallasch, T.J., and Gill, C.J.: Butorphanol and nalbuphine: a pharmacologic comparison, Oral Surg. **59**:15, 1985.

Meperidine

Meperidine is the most frequently used IV narcotic in dentistry. The basic pharmacology of meperidine has been discussed in Chapter 10. After IV administration meperidine will exhibit clinical actions in 2 to 4 minutes. Its duration of action will last approximately 30 to 45 minutes, although considerable variation will occur between patients and with administration of larger doses.

Meperidine has atropine-like properties, having been synthesized in the 1930s as an anticholinergic (see the following paragraph). Patients receiving meperidine may demonstrate decreased salivary secretions and an increased heart rate because of its vagolytic actions. In the doses recommended here, these responses are quite minimal.

Meperidine also produces localized histamine release. This results in the phenomenon of "tracking" at the site of meperidine injection. The skin overlying the vein into which meperidine was injected will appear red, and the patient may mention that itching is present. As the meperidine is carried by the venous blood up the patient's arm toward the heart, the reddening may continue to

Table 25-8. Opioid receptor activation and physiological effects

Mu (μ) receptor	Kappa (κ) Receptor
Euphoria	Sedation
Supraspinal analgesia	Spinal analgesia
Indifference to stimuli	Miosis
Respiratory depression	Limited respiratory depression
Catalepsy	Depressed flexor reflexes
Locomotion	
Hypothermia	
Muscular rigidity	
Dependence	
Sigma (σ) receptor	**Delta (δ) receptor**
Dysphoria	Sedation
Hallucinations	Euphoria
Catatonia	
Mydriasis	
Tachycardia	
Respiratory stimulation	
Vasomotor stimulation	

From Pallasch, T.J., and Gill, C.J.: Butorphanol and nalbuphine: a pharmacologic comparison, Oral Surg. **59**:15, 1985.

follow the path of the vein. It is important to remember that this is a normal response to meperidine administration and not an allergic reaction. Meperidine–induced histamine release will be localized to the path of the vein, whereas an allergic response will be more generalized over the entire region. Management of meperidine–induced histamine release is simply to allow it to dissipate spontaneously, which occurs over the next 10 to 15 minutes.

Dosage. When meperidine is administered intravenously in dental situations the recommended maximal dose is 50 mg. When administered in this dose the usual patient response will be an increased pain reaction threshold (analgesia) without any significant change in the depth of sedation. Narcotics will be administered *following* administration of a sedative-hypnotic (the primary agents for producing sedation). At a maximal dose of 50 mg, meperidine produces virtually no cardiovascular or respiratory depression in the typical patient. Meperidine will always be administered in a concentration not exceeding 10 mg/ml. If the 50 mg/ml concentration is used, 1 ml of meperidine is placed into a 5 ml syringe and 4 ml

of diluent (e.g., 5% dextrose and water) is added. This produces a solution containing 50 ml of meperidine in 5 ml of fluid, or 10 mg/ml.

Availability. Demerol (Winthrop), pethidine 10 mg/ml in 1 ml ampules, 25 mg/ml in 0.5 and 1 ml ampules, 50 mg/ml in 0.5 and 1 ml ampules and 30 ml vials, 75 mg/ml in 1 and 1.5 ml ampules, and 100 mg/ml in 1 and 2.0 ml ampules and 20 and 30 ml vials. Each milliliter of solution contains:

    x mg Meperidine
    pH adjusted to 3.5 to 6.0 with sodium hydroxide or hydrochloric acid

Multiple-dose vials contain 0.1% metacresol as a preservative. No preservatives are added to the ampules.

In my clinical practice with meperidine I have found the 50 mg/ml dosage form the most convenient to work with. The more concentrated forms are potentially dangerous because it is too easy to make a mistake in calculation and administer an overly large dose. The 10 and 25 mg dosage forms are also appropriate; however, with the 10 mg/ml form larger volumes of the agent will be used.

Single–use 1 ml ampules are recommended instead of multiple-dose vials, unless meperidine is used on a regular basis. The 20 or 30 ml vial may become contaminated if permitted to remain unused for a considerable period of time.

Morphine

Morphine sulfate is the classical narcotic agonist. It is rarely used for IV sedation in outpatient situations because of its long duration of action (1½ to 2 hours). The pharmacology of morphine is discussed in Chapter 10.

Dosage. If used for IV sedation in dentistry, the maximal dose of morphine should not exceed 8

MEPERIDINE

The medical history of patients receiving meperidine should be checked for the following:
    Allergy of hypersensitivity to meperidine
    MAO inhibitors taken within 14 days
    Asthma
    COPD and decreased respiratory reserve

MEPERIDINE

Proprietary name	Demerol
Classification	Narcotic agonist
Availability	10, 25, 50, 75, and 100 mg/ml
Average sedative dose	37.5-50 mg
Maximal single dose	50 mg
Maximal total dose	50 mg

MORPHINE

The medical history of patients receiving morphine should be checked for the following:
    Asthma
    Allergy or hypersensitivity to narcotic analgesics
    COPD or decreased respiratory reserve
    MAO inhibitors taken within 14 days

MORPHINE SULFATE

Proprietary name	Morphine
Classification	Narcotic agonist
Availability	2, 4, 8, 10, and 15 mg/ml
Average sedative dose	5-6 mg
Maximal single dose	8 mg
Maximal total dose	8 mg

ALPHAPRODINE

The medical history of patients receiving alphaprodine should be checked for the following:

Allergy or hypersensitivity to narcotics
Asthma
COPD or decreased respiratory reserve
MAO inhibitors taken within 14 days

ALPHAPRODINE

Proprietary name	Nisentil
Classification	Narcotic agonist
Availability	40 and 60 mg/ml
Average sedative dose	15-20 mg
Maximal single dose	30 mg
Maximal total dose	40 mg

---

mg. The drug will be diluted to a concentration of 1 mg/ml prior to use. Little change in the depth of sedation should occur at this dose level, yet the patient's pain reaction threshold will be elevated.

Availability. Morphine sulfate: 2 mg, 4 mg, 8 mg, 10 mg, and 15 mg/ml.

The use of morphine sulfate should be restricted to dental procedures requiring more than 2 hours.

Alphaprodine

Alphaprodine is a rapid onset, short-acting narcotic agonist used primarily in pediatric dentistry by the submucosal route of administration. Its pharmacology has been reviewed in Chapter 10. Onset of action after IV administration is 1 to 2 minutes. Duration of action of intravenously administered alphaprodine is approximately 30 minutes, which makes this a potentially very useful drug in dentistry.

Dosage. The usual IV dose for adults is based on 0.4 to 0.6 mg/kg. For an average 70-mg patient, this provides a dose of 28 to 42 mg. The lower dosage range is recommended initially to properly assess the patient's response. The initial IV dose should not exceed 30 mg, with a maximal total dose of 40 mg recommended.

Availability. Nisentil (Hoffmann-LaRoche): 40 mg/ml in 1 ml ampules and 60 mg/ml in 10 ml vials. Each milliliter of the 1 ml ampule contains:
    40 mg Alphaprodine hydrochloride
    0.875% Citric acid and sodium citrate to adjust pH to 4.6
Each milliliter of the 10 ml vial contains:
    60 mg Alphaprodine hydrochloride
    0.45% Phenol as preservative
    0.875% Citric acid and sodium citrate to adjust pH to 4.6
Caution: the doctor using alphaprodine must be

acutely aware of the difference in drug concentration between the 1 and 10 ml forms. Accidental overdosage might occur should the drug be administered from the multidose vial instead of the 1 ml ampule. *The label of the drug being administered should always be read.*

Fentanyl

Fentanyl is a rapid-onset, short-acting narcotic analgesic that is approximately 100 times more potent than morphine (0.1 mg of fentanyl is equianalgesic to 10 mg of morphine). It was originally synthesized and introduced as one of the components of the combination of drugs known as Innovar (see p. 352).

After IV administration the onset of analgesia and sedation occurs almost immediately (less than 1 minute), although the maximal analgesic and respiratory-depressant effects of fentanyl do not develop for several minutes. Average duration of clinical action is 30 to 60 minutes, which should make fentanyl an almost ideal drug for outpatient procedures requiring approximately 1 hour to complete.

Respiratory depression is a side effect of all narcotic analgesics, with the respiratory-depressant

---

FENTANYL

The medical history of patients receiving fentanyl should be checked for the following:
Allergy or hypersensitivity to narcotics
COPD or decreased respiratory reserve
MAO inhibitors taken within 14 days

FENTANYL

Proprietary name	Sublimaze
Classification	Narcotic agonist
Availability	0.05 mg/ml
Average sedative dose	0.05-0.06 mg
Maximal single dose	0.08 mg
Maximal total dose	0.08 mg

---

effect of fentanyl lasting longer than its analgesic properties. This potential must always be considered prior to discharge of an apparently "recovered" patient from the office in the custody of a person who is not trained to recognize respiratory depression or to manage it.

As is true with other narcotics, fentanyl slows the respiratory rate. This action of fentanyl is rarely observed for more than 30 minutes after the drug's administration. After IV administration of a single dose of fentanyl, peak respiratory depression is noted 5 to 15 minutes later. Depression of breathing (decreased sensitivity to CO_2 stimulation) has been demonstrated for up to 4 hours in healthy volunteers.

Indications. Fentanyl is indicated for use (1) as an analgesic in short anesthetic procedures and in the recovery room; (2) as a narcotic analgesic supplement to general or regonal anesthesia; and (3) in combination with a neuroleptic as a premedication, for the induction of anesthesia, and as an adjunct in the maintenance of general and regional anesthesia.

Contraindications. Fentanyl is contraindicated for use in patients with known allergy or intolerance to it.

Warnings. Fentanyl may cause muscular rigidity, especially involving the muscles of respiration (thoracic and abdominal). This action appears to be related to rate of injection, occurring more frequently when the drug is administered rapidly. This can usually be prevented by the slow IV administration of the drug.

Should muscular rigidity develop, management consists of assisted or controlled ventilation or, if necessary, the administration of a neuromuscular blocking agent such as succinylcholine. This latter step must never be considered unless the doctor has been trained to administer these agents and is thoroughly familiar with the technique of controlled ventilation.

Although a rare complication of fentanyl administration, the potential danger of skeletal muscle rigidity is such that I believe that fentanyl should not be used by a doctor unless she or he has had thorough training in general anesthesia, involving a minimum of 1 full year in an anesthesiology residency training program.

Patients who have received MAO inhibitors within the past 14 days should not receive fentanyl or any other narcotic because of the potential for severe and unpredictable potentiation of the narcotic effect.

The safety of fentanyl in patients under the age of 2 years has not yet been established; therefore, it cannot be recommended for use in the dental outpatient sedation field in this population.

Fentanyl should not be administered to pregnant patients unless the benefits of its administration clearly outweigh the potential hazards of narcotic administration.

Precautions. Fentanyl should be administered with caution to patients with COPD and to patients with decreased respiratory reserve. In these patients the narcotics may decrease respiratory drive to an even greater degree than usual. Liver and renal dysfunction also represent relative contraindications to fentanyl administration.

Adverse reactions. The most frequently noted adverse reactions to fentanyl administration include respiratory depression, apnea, muscular rigidity, and bradycardia. If untreated, these may develop into respiratory arrest, circulatory depression, or cardiac arrest. Other adverse reactions include hypotension, dizziness, blurred vision, nausea and vomiting, laryngospasm, and diaphoresis.

Dosage. Fentanyl is administered in conjunction with other antianxiety/sedative-hypnotic medications for sedation. The recommended dose of fentanyl is therefore predicated on the fact that the patient has already received one or more

other CNS depressants. The maximal dose of fentanyl recommended for use in outpatient sedative procedures is 0.05-0.06 mg (1.0 to 1.2 ml). This dose is equivalent to 8 mg morphine and about 50 mg of meperidine.

Fentanyl should always be diluted from its initial concentration of 0.05 mg/ml by adding 4 ml of diluent (e.g., 5% dextrose & water) to produce a final concentration of 0.01 mg/ml.

Availability. Sublimaze (Janssen) (McNEILAB): 0.05 mg/ml in 2 and 5 ml ampules. Each milliliter of solution contains:

0.05 mg Fentanyl citrate
Sodium hydroxide for adjustment of pH to 4.0 to 7.5

Fentanyl use in outpatient procedures should be restricted to those doctors with training in general anesthesia and management of the airway of the unconscious patient.

NARCOTIC AGONIST/ANTAGONISTS

Because of the significant side effects of the narcotic agonists considerable research has been conducted in an effort to find a potent analgesic drug that possesses the efficacy of morphine but lacks the respiratory-depressant characteristic, drug dependence, and abuse liability of morphine.

In the 1960s some success was attained with the introduction of pentazocine, the first drug with both narcotic agonist and narcotic antagonist properties to be marketed (1967). In the succeeding years some of the initial fervor for pentazocine has waned as some significant side effects have been found. Two other drugs in this same category—nalbuphine and butorphanol—have recently been made available and are beginning to gain increased popularity in IV sedation in both dental and medical outpatient procedures. The three agents classified as narcotic agonist/antagonists are pentazocine, nalbuphine, and butorphanol.

Pentazocine

The chemical formula for pentazocine is 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol lactate. Pentazocine was introduced in 1967 as a *nonnarcotic narcotic* in both oral and parenteral formulations.

A dose of 30 mg of pentazocine is equivalent to approximately 10 mg of morphine or 75 mg of meperidine. When administered intravenously the onset of action of pentazocine is 1 to 2 min-

---

> **PENTAZOCINE**
>
> The medical history of patients receiving pentazocine should be checked for the following:
> Allergy to pentazocine
> Suspected drug dependence
> Prior adverse CNS reaction to pentazocine
> Asthma
> COPD or decreased respiratory reserve

---

utes with a duration of action of approximately 1 hour, although the patient may still exhibit alterations of consciousness for a number of hours after discharge from the office.

Pentazocine has narcotic antagonist effects as well as sedative properties. Administered to patients receiving morphine-type opioids, pentazocine weakly antagonizes the analgesic, cardiovascular, respiratory, and CNS–depressant effects produced by these agents. The sedative effect produced by a 30 mg IV dose of pentazocine is equivalent to approximately 10 mg diazepam administered intravenously. Pentazocine, however, does not provide the same degree of amnesia as does diazepam.

Pentazocine is indicated for use in the management of moderate to severe pain (usually administered orally or intramuscularly), as well as preoperative or preanesthetic medication (usually administered intramuscularly), and as a supplement during general anesthesia (administered intravenously). It has also gained some use within dentistry as a substitute for the narcotic agonists.

Contraindications. Pentazocine is contraindicated for use in patients with documented allergy to it.

Warnings. Despite earlier claims to the contrary, experience with pentazocine has demonstrated that both psychological and physical dependence can develop. Abrupt discontinuance of pentazocine has produced a clinical syndrome exhibiting abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Pentazocine has become a drug with significant abuse potential, being combined (orally) with the antihistamine pyribenzamine in a combination called "Ts and blues."

Just recently the manufacturers of oral penta-

<div style="border:1px solid">

PENTAZOCINE

Proprietary name	Talwin
Classification	Narcotic agonist/ antagonist
Availability	30 mg/ml
Average sedative dose	20 mg
Maximal single dose	30 mg
Maximal total dose	30 mg

</div>

zocine (Talwin) reformulated its compound, taking into account this abuse potential. Its new formulation, Talwin Nx, is a combination of pentazocine (50 mg) with the narcotic antagonist naloxone (0.5 mg). The intent of this combination is obvious, but its effectiveness is not yet known.

Pentazocine should only be used in the pregnant patient if the benefits of administration clearly outweigh its potential hazards. For routine outpatient sedation in the typical dental setting, there is little indication for pentazocine administration in pregnant patients.

Another of the significant untoward effects of pentazocine has been the occurrence of acute neuropsychiatric manifestations, such as visual hallucinations, disorientation, confusion, mental depression, disturbing dreams, and dysphoria. These responses have resolved spontaneously within a few hours. The mechanism responsible for them is as yet unknown. Management of reactions that do occur is symptomatic, with vital signs being monitored and recorded on a regular basis during the reaction. Readministration of pentazocine to this same patient at future dates should be avoided if at all possible to minimize the possibility of recurrence.

The administration of pentazocine to patients under the age of 12 years is not recommended because of a lack of clinical data. The drug package insert for pentazocine recommends that ambulatory patients receiving parenteral pentazocine be cautioned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions. Patients with asthma, COPD, or other conditions exhibiting decreased respiratory reserve should be given pentazocine with caution.

Patients with extensive liver disease appear to exhibit a greater number of adverse side effects from the usual clinical dose, a response indicating a decreased rate of metabolism of the drug by the liver. The plasma half-life of pentazocine is approximately 2 hours.

Pentazocine should be administered with caution to patients with seizure disorders. Seizures have developed after administration of pentazocine, although a direct cause and effect relationship has never been established.

Adverse reactions. Pentazocine demonstrates the same adverse reactions as the narcotic agonists previously discussed, including nausea and vomiting, xerostomia, diarrhea, constipation, blurred vision, euphoria, dysphoria, respiratory and cardiovascular depression, and allergic reactions. In addition pentazocine produces the neuropsychiatric reactions noted earlier (p. 343).

Dosage. Pentazocine is used in conjunction with an antianxiety/sedative-hypnotic agent for the production of sedation. It is, therefore, administered after the patient has received one or more agents. The maximal recommended dose of pentazocine in IV sedation procedures is 30 mg. When titrated slowly, the usual dose required (in combination with other drugs) is approximately 20 mg.

Availability. Talwin (Winthrop): 30 mg/ml in 1 ml, 1.5 ml, and 2 ml ampules and in 10 ml vials. Each milliliter of solution in the ampule contains:

30 mg Pentazocine lactate
1 mg Acetone sodium bisulfite
2.2 mg Sodium chloride
Water for injection

Each milliliter of solution in the vial contains:

30 mg Pentazocine lactate
2 mg Acetone sodium bisulfite
1.5 mg Sodium chloride
1 mg Methyl paraben as preservative
Water for injection

The pH of both solutions is adjusted to 4 to 5 with lactic acid or sodium hydroxide. Air in both the ampules and vials has been displaced with N_2.

Nalbuphine

Nalbuphine—17-(cyclobutylmethyl)-4,5α-epoxymorphinan-3,6α,14-triol, hydrochloride—was synthesized in 1965. The chemical incorporates the molecular features of the narcotic agonist oxymorphone hydrochloride (Numorphan) with that of the narcotic antagonist naloxone hydrochloride (Narcan).

Pharmacology. Nalbuphine is a potent analgesic with analgesic potency approximately 0.8 to 0.9

times that of morphine. In clinical practice nalbuphine is considered to be equianalgesic to morphine when administered in equal doses (e.g., 10 mg of nalbuphine is equal to 10 mg of morphine).

After IV administration the onset of action of nalbuphine is 2 to 3 minutes. Its duration of action is slightly longer than that of morphine (approximately 3 to 6 hours). A 10 mg dose of nalbuphine is equivalent to approximately 50 to 75 mg of meperidine.

Studies of the effectiveness of nalbuphine as a preoperative sedative agent are lacking, and there is very little information about the use of nalbuphine in dental procedures. To date I have used nalbuphine approximately 30 times in IV procedures on dental outpatients with good results (see below).

Nalbuphine possesses narcotic antagonist effects at the mu opioid receptor. Nalbuphine is 10 times as effective as pentazocine as a narcotic antagonist and one-fourth as potent as nalorphine in morphine-dependent subjects. Quite interesting, and potentially very significant, is the fact that nalbuphine may be used as a narcotic antagonist in place of naloxone. Magruder et al. (1982) substituted nalbuphine (0.1 mg/kg) for naloxone to reverse respiratory depression produced by oxymorphone or hydromorphone. They noted a dramatic reversal of the respiratory depression and a restoration of normal ventilation within 5 minutes. Of greater importance is the fact that nalbuphine provided substantial analgesia after the reversal of the narcotic-induced respiratory depression, which extended well into the postoperative period. This differential mu (opioid antagonism) and kappa (agonist analgesia) opioid receptor actions of nalbuphine may be of use in avoidance of the adverse cardiovascular stimulation sometimes observed in patients suffering from pain when naloxone is administered to reverse narcotic-induced CNS depression; unfortunately, however, it also acts to reverse the analgesia produced by the narcotic.

Although not yet recommended as the drug of choice for reversal of narcotic–induced respiratory depression (more research data are necessary), nalbuphine is being increasingly used in place of naloxone for this purpose.

Pharmacokinetics. After IV administration the analgesic effects of nalbuphine appear in 2 to 3 minutes. The analgesic effects of the drug last for approximately 3 to 6 hours. The plasma half-life of nalbuphine is 5 hours. The drug undergoes metabolism in the liver; oral doses of nalbuphine

---

NALBUPHINE
The medical history of patients receiving nalbuphine should be checked for the following:
Allergy or hypersensitivity to nalbuphine
History or suspicion of drug dependence
Pregnancy or child-bearing potential
Asthma, COPD, or other types of decreased respiratory drive

---

undergo a significant hepatic first-pass effect, with only 20% of an orally administered dose being biologically available.

Nalbuphine is physically compatible with most aqueous drugs and can thus be combined in the same syringe. Nalbuphine cannot, however, be combined with either diazepam or pentobarbital because a milky white precipitate forms.

Adverse effects. When used solely as an analgesic, the most frequently noted adverse effect is sedation, which is reported in 36% of patients treated with nalbuphine. This *side effect* may be used to advantage in IV sedation procedures. Other common adverse responses (occurring in more than 3% of patients) include the following:

Sweaty, clammy feeling	9%
Nausea and vomiting	6%
Dizziness, vertigo	5%
Dry mouth	4%
Headache	3%

Psychotomimetic effects occurred only rarely and included depression, confusion, dysphoria, euphoria, feelings of unreality, feelings of hostility, and hallucinations. The incidence of these is significantly less than that seen with pentazocine.

Possibly the most potentially serious adverse effect of nalbuphine administration is respiratory depression. When the typical narcotic agonists are administered, both the rate and depth of respiration are depressed until apnea ensues. For outpatient ambulatory procedures, respiratory depression is the factor that most limits the use of narcotics. Nalbuphine possesses ceiling effects for respiratory depression, whereas its analgesic effects may become more pronounced with increasing doses. Gal et al. (1982) demonstrated a plateau effect for both respiratory depression and analgesia for nalbuphine at doses up to 0.6 mg/kg. In several other studies it has been demon-

```
┌─────────────────────────────────────┐
│                                     │
│           NALBUPHINE                │
│                                     │
│  Proprietary name      Nubain       │
│  Classification        Narcotic agonist/ │
│                          antagonist │
│  Availability          10 mg/ml     │
│  Average sedative dose 7-8 mg       │
│  Maximal single dose   10 mg        │
│  Maximal total dose    10 mg        │
│                                     │
└─────────────────────────────────────┘
```

strated that the normal dose of nalbuphine (7 to 10 mg/70 kg) produces the same degree of respiratory depression as an equivalent dose of morphine; however, the nalbuphine-induced respiratory depression peaked at 30 mg/70 kg (equivalent to 20 mg/70 kg morphine) and remained the same even at nalbuphine doses of 3mg/kg (210 mg/70 kg).

Larger doses of nalbuphine do not extend the duration of respiratory depression beyond the usual 3 hours. Nalbuphine therefore possesses a ceiling effect to both the degree and duration of respiratory depression. This is in contrast to butorphanol, which has a ceiling effect only for the degree of respiratory depression, but not its duration.

In the area of administration to medically compromised patients, especially the cardiovascular risk, nalbuphine produces a slight decrease in the cardiac workload, a potentially beneficial effect. Romagnoli and Keats considered nalbuphine an ideal drug for patients with heart disease since it was devoid of hemodynamic effects except those following the relief of pain and anxiety.

One of the potential benefits of the narcotic agonist-antagonist analgesics is a limited or absent drug dependence and abuse liability (psychic dependence, physical dependence, tolerance) as a result of their opioid antagonist actions when compared to complete mu-receptor agonists such as morphine. It appears at this point that this hope is fulfilled to some extent with nalbuphine and butorphanol.

Overdosage. Overdose of nalbuphine is exceptionally rare but potentially possible. Signs and symptoms of overdose would include CNS depression and respiratory depression, both of which may be completely reversed with the IV administration of naloxone.

Contraindications. Nalbuphine is contraindicated for use in patients who are allergic or hypersensitive to it.

Warnings. Because nalbuphine produces CNS depression, patients receiving this drug must be cautioned against the performance of potentially dangerous tasks such as driving a car and operating machinery.

Nalbuphine is not recommended for administration to patient's under the age of 18 years because of a lack of clinical experience in patients in this age group.

Pregnant patients should not receive nalbuphine unless the advantages of its administration clearly outweigh its potential disadvantages.

Nalbuphine may exhibit additive effects with other CNS depressants administered concurrently. The dosage of one or both of the drugs should be reduced.

Precautions. Nalbuphine should be administered with caution, and at reduced doses, to patients with impaired respiratory drive, including asthma and COPD.

Because nalbuphine is metabolized in the liver and excreted through the kidneys, it is possible that patients with impaired hepatic or renal function may overrespond to the usual dose of the drug. Doses should be reduced in these patents. Titration will minimize this possibility.

Dosage. When administered intravenously, nalbuphine should be titrated to clinical effect. The maximal dose of nalbuphine recommended for IV sedative procedures is 10 mg. This also represents the maximal single and total doses. Onset of action after IV administration is 2 to 3 minutes, with a duration of analgesic effect of 3 to 6 hours. The average IV dose for nalbuphine has been 7 to 8 mg in my limited clinical experience with it.

When administered after administration of diazepam, the depth of sedation is rarely increased with nalbuphine; however, recovery is somewhat less complete than that observed when diazepam is administered alone.

Because of the doses recommended here, the beneficial effects of nalbuphine on minimizing respiratory depression will not be observed. It is only at doses considerably greater than these that the diminished respiratory depression is noted. In doses up to 10 mg the degree of respiratory depression should not be profound but will be equivalent to that produced by 10 mg of morphine or 50 to 75 mg of meperidine.

Availability. Nubain (Endo): 10 mg/ml in 1 ml and 2 ml ampules and 10 ml vials. Each milliliter of solution contains:

10 mg Nalbuphine hydrochloride
0.1% Sodium chloride
0.94% Sodium citrate
1.26% Citric acid anhydrous
0.1% Sodium metabisulfite
0.2% 9:1 Mixture of methylparaben and pro-
 pylparaben as a preservative
Hydrochloric acid to adjust pH

Butorphanol

Butorphanol was synthesized in 1971 by Mon-
kovic and introduced in 1978. Butorphanol is a
synthetic agonist/antagonist analgesic, similar in
pharmacology to nalbuphine. The chemical formu-
la of butorphanol is levo-N-cyclobutylmethyl-6,
10αβ-dihydroxy-1,2,3,9,10,10a-hexahydro-(4H)-
10, 4a-iminoethanophenanthrene tartrate.

Pharmacology. Comparing butorphanol to mor-
phine for analgesia 2 mg of butorphanol (admin-
istered intramuscularly) is approximately as effec-
tive as 10 mg of morphine, 80 mg of meperidine,
and 40 mg of pentazocine. Data indicate that bu-
torphanol is approximately 3.5 to seven times as
potent as morphine; 15 to 20 times more potent
than pentazocine; and 30 to 40 times more potent
than meperidine on a weight basis.

Pharmacokinetics. After IV administration, an-
algesic properties develop within minutes. Maxi-
mal blood levels occur in 5 minutes and thereafter
decline in a biphasic manner. The α–half-life of
rapid elimination (distribution) is approximately
0.1 hour, and the β–half-life (metabolism and ex-
cretion) is 2.15 to 3.5 hours. Duration of analgesic
properties is 3 to 4 hours.

Butorphanol undergoes extensive metabolism
in the liver prior to excretion through the kid-
neys. Less than 5% of a dose is excreted un-
changed in the urine. The major route of elimi-
nation of butorphanol and its metabolites is
through the kidney (75%), with biliary excretion
accounting for 15% of the dose. It is 80% bound
to human serum protein and distributed exten-
sively to tissues. Butorphanol is highly lipid solu-
ble and concentrates in adipose tissue and excre-
tory organs. Cumulation may occur with repeated
doses of the drug.

Effect on respiration. Butorphanol has proper-
ties similar to those of pentazocine and nalbu-
phine with respect to respiratory depression and
opioid antagonist properties. As an antagonist bu-
torphanol is 30 times as potent as pentazocine but
only one-fortieth as potent as naloxone. In a study
by Nagashima et al. (1976), 2 and 4 mg IV doses
of butorphanol were compared to 10 and 20 mg

BUTORPHANOL

The medical history of patients receiving
butorphanol should be checked for the follow-
ing:
 Allergy or hypersensitivity to butorphanol
 Known or suspected narcotic dependence
 Asthma, COPD, or decreased respiratory re-
  serve
 High blood pressure
 Cardiovascular disease

---

doses of morphine. Respiratory depression pro-
duced by 4 mg of butorphanol was found to be
statistically and clinically equivalent to that pro-
duced by 2 mg of butorphanol or 10 mg of mor-
phine. This as well as other studies has demon-
strated that butorphanol does not produce a dose-
related effect on respiration in contrast to that ob-
served with narcotic agonists such as morphine
and meperidine.

Increasing doses of butorphanol did, however,
produce a longer duration of respiratory depres-
sion, although the degree of depression did not
increase. Butorphanol possesses a ceiling effect
only for the degree of respiratory depression, but
not for its duration whereas nalbuphine possesses
a ceiling effect for both the depth and duration of
respiratory depression. As with other narcotic ag-
onists and narcotic agonist/antagonists, these res-
piratory-depressant properties of butorphanol are
reversible with naloxone.

Cardiovascular effects. Unlike nalbuphine, bu-
torphanol does possess cardiovascular effects sim-
ilar to, but less intense than, those of pentazocine.
These include increased pulmonary artery pres-
sure, increased pulmonary wedge pressure, in-
creased left ventricular end-diastolic pressure, in-
creased systemic arterial pressure, and increased
pulmonary vascular resistance. Both the cardiac
index and cardiac workload are increased with
butorphanol.

Butorphanol, as well as pentazocine, adminis-
tration should be restricted in patients with acute
myocardial infarction, coronary insufficiency or
ventricular dysfunction, and high blood pressure.

Butorphanol, like nalbuphine, is an agonist/
antagonist analgesic with a low physical-depen-
dence liability, which distinguishes it from tradi-
tional potent narcotics.

When administered in large doses the incidence

BUTORPHANOL

Proprietary name	Stadol
Classification	Narcotic agonist/
	antagonist
Availability	1 and 2 mg/ml
Average sedative dose	1.5 mg
Maximal single dose	2 mg
Maximal total dose	2 mg

---

of unpleasant psychotomimetic effects is increased. This factor may serve to limit the abuse potential of this drug. Only time will tell, however, if these optimistic forecasts for both butorphanol and nalbuphine are correct.

Side effects. Side effects reported after butorphanol administration are similar to those for other parenteral analgesics. The most frequently reported side effect was sedation (37%), a side effect that may be used to advantage during IV administration of the drug. Other common side effects were:

Nausea	7%
Clamminess sweating	5%
Headache	2%
Vertigo	2%
Floating, pleasant feelings	2%
Dizziness	2%
Lethargy	2%

Overdosage. Overdose of butorphanol is extremely unlikely to develop; however, it is a clinical possibility. Signs and symptoms will relate to exaggerated CNS and respiratory depression. Management consists of basic life support, with consideration for airway patency and ventilation, followed by the administration of naloxone or other opioid antagonists.

Warnings. Because of its opioid antagonist properties, the use of butorphanol is not recommended in patients known to be physically dependent on narcotics. Administration in such patients may induce an acute abstinence syndrome (withdrawal).

Because of the increased workload of the heart occurring with butorphanol administration, this drug is not recommended in patients with ventricular dysfunction or coronary insufficiency.

Precautions. Because butorphanol produces some respiratory depression, it should be administered with caution to patients with preexisting respiratory depression, such as patients receiving other CNS depressants, patients with asthma, COPD, or other types of decreased respiratory reserve, or patients with high blood pressure.

Patients with hepatic or renal dysfunction may overrespond to usual doses of butorphanol. If used in these patients the dosages should be adjusted to account for this possibility. With IV administration, slow titration will minimize this possibility.

Use of butorphanol in patients under 18 years of age or in pregnant patients is not recommended because of a lack of clinical experience to indicate its safety in these groups.

Ambulatory patients receiving butorphanol must, of course, be cautioned against possible hazardous situations such as driving a car or operating machinery.

Dosage. My experience with butorphanol administered for IV sedation has been limited to approximately 50 cases at this time (November 1984). However, it has been my impression that this agent may effectively be substituted for the traditional narcotic agonists with no decrease in effectiveness and with the possible addition of decreased risk of respiratory depression. The doses recommended for IV use should preclude significant respiratory depression regardless of the pharmacological properties of butorphanol.

After IV administration of 1 to 2 mg, onset of analgesic and sedative effects is quite rapid (1 to 2 minutes). Administered after diazepam, titrated butorphanol usually will not produce a deepening of the sedative level of the patient; therefore, the maximal recommended dose (2 mg) is usually given. Recovery from diazepam-butorphanol sedation is not as complete clinically as from diazepam sedation alone.

Availability. Stadol (Bristol): 1 mg/ml in 1 mg single-dose vial and 2 mg/ml in 1, 2, and 10 ml vials. Each milliliter of solution contains sodium chloride, sodium citrate, and citric acid as buffers. The 10 ml multidose vial also contains the preservative benzethonium chloride.

The narcotic agonist/antagonist drugs offer considerable advantages when compared to the traditional narcotic agonists such as meperidine, alphaprodine, fentanyl, and morphine. Whereas respiratory depression was a significant factor in drug administration, this risk has been reduced (although not eliminated). Problems can still develop with administration of these newer agents,

but they appear to be less likely to occur.

Pentazocine has been available for more than a decade. Its use intravenously in sedation is not very common, primarily because of the significant incidence of negative psychotomimetic effects. In addition it is known today that physical dependence to pentazocine does occur.

Butorphanol, a more recent addition to the armamentarium, to date appears to have fewer significant adverse effects than pentazocine; however, it does produce an increase in cardiovascular workload, which contraindicates its use in the patient at cardiovascular risk.

Nalbuphine appears to have all the advantages of butorphanol, with the additional advantages of not increasing the cardiovascular workload and of being an excellent narcotic antagonist (see p. 344).

One additional benefit of butorphanol and nalbuphine is that they are nonscheduled drugs, not requiring special forms or paperwork for their purchase or administration. Pentazocine is a schedule IV drug, whereas the narcotic agonists are schedule II drugs.

Clinical experience must be gained with these newer drugs before definitive statements can be made as to their applicability to dentistry.

NARCOTIC ANTAGONIST

The only drug presently available that possesses pure opioid-antagonist properties is naloxone. The pharmacology and clinical importance of this drug will be reviewed in the section on antidotal drugs (p. 357).

ANTICHOLINERGICS

The anticholinergics, also known as belladonna alkaloids and cholinergic blocking agents, are important drugs in the practice of anesthesia, as well as being valuable adjuncts to intravenously administered sedative medications. In the practice of anesthesia and in IV sedation the indications for use of the anticholinergics are (1) as preoperative medication to reduce salivary secretions; (2) to correct vagally induced bradycardia; and (3) to reverse curarization (general anesthesia) when administered with neostigmine. Three drugs—atropine, scopolamine, and glycopyrrolate—will be discussed. These agents are very popular during IV sedation in dentistry, being administered primarily for their antisalivary actions.

Pharmacology. The belladonna alkaloids are widely distributed in nature. Atropine, chemically a racemic mixture of levo- and dextro- hyoscy-amine (only the levo form is pharmacologically active), is found in the following botanicals:

Atropa belladonna—known as the deadly nightshade

Datura stramonium—Jamestown weed, jimson weed, stinkweed, thorn-apple, and devil's apple

Scopolamine, chemically levo-hyoscine, is found in the following:

Hyoscyamus niger—black henbane
Scopolia carniolica

Glycopyrrolate is a synthetic anticholinergic compound that was introduced in 1961. It is a quaternary ammonium compound with the chemical name 1-methyl-3-pyrrolidyl-phenyl-cyclopentane-glycolate methobromide.

Mechanism of action. The anticholinergics act as competitive antagonists to acetylcholine at the postganglionic receptor located at the neuroeffector junction of the parasympathetic nervous system.

Although the actions of these drugs are essentially similar, the degree to which the individual drug possesses a certain property may differ. For example, scopolamine has a greater effect on the salivary glands than does atropine, but atropine has a greater effect on the heart and bronchial musculature. In clinical doses atropine does not produce CNS depression; however, scopolamine does and is therefore used quite commonly for preoperative medication.

Central nervous system. Atropine produces a stimulation of the medulla and higher cerebral centers. In clinical doses of 0.5 to 1.0 mg this effect is noted as a mild vagal stimulation in which both the rate and depth of breathing are increased. This effect is probably a result of bronchiolar dilation and increased physiological dead space. Atropine is *not* an effective agent in reversing serious respiratory depression.

Scopolamine in therapeutic doses produces a degree of CNS depression, clinically noted as drowsiness, euphoria, amnesia, fatigue, and dreamless sleep. Unfortunately in some patients the same clinical dose may produce excitement, restlessness, hallucinations, and delirium. This is particularly likely to occur in the presence of pain.

Glycopyrrolate, being a quaternary ammonium compound, does not cross the blood-brain barrier and does not produce the CNS actions noted in the preceding paragraphs for atropine and scopolamine.

In cases in which sedation is a desirable effect,

the administration of scopolamine is preferred to either atropine or glycopyrrolate. Scopolamine provides five to 15 times the sedative effects of the other two agents.

Amnesia may be another desirable action of an anticholinergic drug. Of the three drugs mentioned, only scopolamine is capable of producing this effect. Although amnesia may occur after scopolamine administration, it is not as consistent a finding as occurs with diazepam or midazolam. When present, however, amnesia tends to be prolonged, often persisting for 2 to 4 hours. Although anterograde amnesia—lack of recall of events occurring after administration of scopolamine—is most common, retrograde amnesia—lack of recall of events occurring prior to administration of the drug—may also occur.

Eye. The anticholinergics block the responses of the sphincter muscle of the iris and the ciliary muscle of the lens to cholinergic stimulation. They therefore produce mydriasis (dilation of the pupil) and cycloplegia (paralysis of accommodation). Fortunately therapeutic doses of atropine (0.4 to 0.6 mg) produce little ocular effect. However, scopolamine in therapeutic doses produces significant mydriasis and cycloplegia.

The anticholinergic drugs, when administered parenterally, have little effect on intraocular pressure, except in patients with *acute narrow-angle glaucoma,* in whom dangerously high pressures may develop. This occurs when the iris, which is crowded back into the angle of the anterior chamber of the eye, interferes with drainage of the aqueous humor. In the more commonly seen wide-angle glaucoma, such an increase in intraocular pressure seldom occurs and these agents may be used with little increase in risk to the patient.

The administration of these agents is contraindicated for patients who wear contact lenses.

Respiratory tract. The anticholinergic drugs decrease secretions of the nose, mouth, pharynx, and bronchi, thereby drying the mucous membranes of the respiratory tract. This of course represents one of the indications for administration of these drugs as preanesthetic medications. Clinically the antisialic actions of 0.4 mg atropine are equal to a dose of 0.2 mg glycopyrrolate.

Bronchial smooth muscle is also dilated with administration of these drugs, atropine being considerably more potent in this regard than either scopolamine or glycopyrrolate.

Atropine, scopolamine, and glycopyrrolate decrease the occurrence of laryngospasm during general anesthesia. This is because of the decrease in respiratory tract secretions that might precipitate reflex laryngospasm, which is produced by contraction of the laryngeal skeletal muscle.

Cardiovascular actions. The main effect of the anticholinergics on the heart is to alter its rate. When used in clinical doses of 0.4 to 0.6 mg, atropine will produce a decrease in heart rate of 4 to 8 beats/minute. This effect is not seen if the drug is administered *rapidly* intravenously. Larger doses produce a tachycardia by blocking the effects of the vagus nerve at the S-A pacemaker. The rate may rise as much as 35 to 40 beats above the resting rate (in a study with young men receiving 2 mg of atropine intramuscularly). This action of the anticholinergics is most notable in young healthy adults in whom vagal tone is great. In very young patients and geriatric patients atropine may fail to accelerate the heart rate.

Scopolamine in small doses, 0.1 to 0.2 mg, produces even more profound cardiac slowing than atropine. With higher doses the tachycardia is equal to that of atropine but is shorter lived. The rate will return to baseline or perhaps result in a bradycardia.

Glycopyrrolate produces less tachycardia than do atropine or scopolamine and thus is indicated for use in patients in whom atropine- or scopolamine-induced tachycardias are not desirable. Conversely, in situations in which significant bradycardia has developed, the administration of glycopyrrolate will not provide the desired increase in heart rate. Atropine or scopolamine will be required at this time.

Gastrointestinal tract. Therapeutic doses of anticholinergics do not greatly affect gastric secretion. Doses in excess of 1 mg (atropine) must be administered to significantly alter gastric secretion. These drugs have little effect on the secretion of pancreatic juice, bile, or succus entericus.

On the other hand, the anticholinergics have profound actions on gastrointestinal motility. In both healthy patients and patients with gastrointestinal disease, therapeutic doses of the anticholinergics inhibit the motor activity of much of the small and large intestine. Motility is reduced along with muscle tone, as well as the amplitude and frequency of peristaltic activity. This is termed the *antispasmodic effect* of the anticholinergics.

Secretory glands. The actions of the anticholinergics on respiratory and digestive tract secretions have been discussed. Even small doses of

these drugs inhibit the activity of sweat glands. The skin becomes hot and dry. If sweating is depressed enough, the body temperature may rise, but this is usually noted only after toxic doses.

The lacrimal glands are also inhibited by the anticholinergics, but to a smaller extent than other secretory glands.

The secretion of milk is not significantly affected.

Biotransformation. The anticholinergics are rapidly removed from the blood and are distributed throughout the body. Atropine is approximately 50% protein bound in the blood.

The metabolism of the anticholinergics is not very well understood at this time. Approximately 13% to 50% of a dose of atropine is found unchanged in the urine. The liver is the primary organ of biotransformation. A small amount of the drug is found in the feces, and an even smaller amount is found in expired air.

Less than 1% of a dose of scopolamine is recovered unchanged in the urine.

Atropine

In clinical doses (0.5 to 1.0 mg), atropine produces stimulation of the medulla and higher cerebral centers, resulting in a mild central vagal stimulation and moderate respiratory stimulation. Its primary IV use is for the reduction of salivary and bronchial secretions.

Contraindications to the administration of atropine include glaucoma, adhesions (synechiae) between the iris and the lens of the eye, and asthma.

The effects of atropine on the developing fetus are not known with any degree of certainty; therefore, the use of atropine in the pregnant patient should be reserved for those cases in which its effects are truly important. In general this will rule out its use in dental situations.

Adverse reactions. Although systemic tolerance to drug effects varies greatly, the following is the "normal" response to increasing doses of atropine:

Dose (mg)	Effect
0.5	Slight dryness of nose and mouth Bradycardia
1.0	Greater dryness of nose and mouth, with thirst Slowing, then acceleration, of the heart Mydriasis
2.0	Very dry mouth Tachycardia with palpitation Mydriasis Slight blurring of near vision Flushed, dry skin

Dose (mg)	Effect
5.0	Increase in the preceding symptoms plus the following: Disturbance of speech Difficulty in swallowing Headache Hot, dry skin Restlessness with asthenia (lack of energy)
10.0	The preceding symptoms to an extreme degree plus the following: Ataxia Excitement Disorientation Hallucinations Delirium Coma

Intoxication to atropine has been described as follows: "Dry as a bone, red as a beet, and mad as a hatter." Fortunately, atropine intoxication is rarely fatal if rapidly diagnosed and antidotal therapy instituted. Physostigmine— 1 to 5 ml of a dilution of 1 mg physostigmine in 5 ml (0.2 mg/ml) administered intravenously—is the drug of choice in management of this reaction. The dose

---

ATROPINE SULFATE

The medical history of patients receiving atropine sulfate should be checked for the following:
- Glaucoma
- Prostate disease
- Asthma
- Adhesions between iris and lens of eye
- Myasthenia gravis
- Contact lenses

ATROPINE SULFATE

Classification	Anticholinergic
Availability	0.3-1.3 mg/ml
Average therapeutic dose	0.4-0.6 mg
Maximal single dose	0.4-0.6 mg
Maximal total dose	0.4-0.6 mg

may be repeated every 5 minutes if necessary for a total dose of 2 mg in children and 6 mg in adults.

Dosage. The usual adult dose of atropine is 0.4 to 0.6 mg. In children the following doses are recommended:

Weight (pounds)	Dose (mg)
7-16	0.1
17-24	0.15
25-40	0.2
41-65	0.3
66-90	0.4
More than 90	0.4-0.6

Availability. Atropine sulfate: 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 1.0 mg, and 1.3 mg/ml. Each milliliter of atropine sulfate solution contains:

0.4 mg Atropine sulfate
0.5% Chlorobutanol as a preservative

Scopolamine hydrobromide

Scopolamine hydrobromide differs in several significant ways from atropine. It can produce a degree of CNS depression, whereas atropine does not. Scopolamine is a frequently used constituent of preanesthetic medication. In this regard scopolamine provides the following three beneficial effects:

Decreases in salivary and bronchial secretions
Some sedative effect (minor)
Anterograde amnesia

The second and third effects are unique to scopolamine and form the basis for its widespread use in anesthesia practice. Scopolamine is also unfortunately more apt to produce a phenomenon known as *emergence delirium* than is atropine or glycopyrrolate. Since this reaction, which involves vivid dreams, nightmares, and hallucinations, develops most often in very young and elderly patients, the use of scopolamine in patients under the age of 6 years and over the age of 65 years is discouraged.

Dosage. The usual adult therapeutic dose is 0.32 to 0.65 mg. The following dosage scale is recommended for children:

Age	Dose (mg)
6 months to 3 years	0.1 -0.15
3-6 years	0.15-0.2
6-12 years	0.2 -0.3

Availability. Scopolamine hydrobromide: 0.3 mg/ml; 0.4 mg/ml in 0.5 and 1.0 ml ampules; and 0.6 mg/ml. Each milliliter of scopolamine hydrobromide solution contains:

0.3 mg scopolamine hydrobromide
1% alcohol
10% mannitol
Water for injection

SCOPOLAMINE HYDROBROMIDE

The medical history of patients receiving scopolamine hydrobromide should be checked for the following:
Glaucoma
Adhesions between iris and lens
Asthma
Prostatic disease
Myasthenia gravis
Contact lenses

SCOPOLAMINE HYDROBROMIDE

Classification	Anticholinergic
Availability	0.3-0.6 mg/ml
Average therapeutic dose	0.3 mg
Maximal single dose	0.3 mg
Maximal total dose	0.3 mg

Glycopyrrolate

Glycopyrrolate is the most recent addition to the anticholinergic armamentarium. Because it is a quaternary ammonium compound, glycopyrrolate will not cross lipid membranes, such as the blood-brain barrier. This is in contrast to both atropine and scopolamine. Glycopyrrolate is unlikely to produce unwanted CNS depression or delirium-type reactions

After IV administration the onset of clinical activity develops within 1 minute. Glycopyrrolate has a duration of action of vagal blocking effects for 2 to 3 hours and antisialagogue effects for up to 7 hours. This latter effect may be deleterious in the ambulatory patient.

Warnings. Ambulatory patients receiving glycopyrrolate must be advised not to perform hazardous work, operate machinery, or drive a motor ve-

---

GLYCOPYRROLATE

The medical history of patients receiving glycopyrrolate should be checked for the following:
  Allergy to glycopyrrolate
  Glaucoma
  Prostatic disease
  Asthma
  Myasthenia gravis
  Ischemic heart disease
  Contact lenses

GLYCOPYRROLATE

Proprietary name	Robinul
Classification	Anticholinergic
Availability	0.2 mg/ml
Average therapeutic dose	0.1 mg
Maximal single dose	0.1 mg
Maximal total dose	0.2 mg

---

hicle, since the drug may produce drowsiness or blurred vision.

In the presence of a high environmental temperature, heat prostration (heat stroke and fever caused by decreased sweating) can occur with the use of glycopyrrolate.

Precautions. Glycopyrrolate should be used with caution in patients with tachycardia since the drug may cause a further increase in the heart rate. In addition patients with ischemic heart disease, coronary artery disease, heart failure, arrhythmias, hypertension, or hyperthyroidism should be evaluated carefully prior to administration of glycopyrrolate.

Although glycopyrrolate has been shown to be nonteratogenic in animal studies, its effect on the human fetus is unknown; therefore, the use of glycopyrrolate in pregnant patients is not recommended and should be reserved for those cases in which its effects are required.

Dosage. The usual therapeutic dose of glycopyrrolate in adults is 0.01 mg (0.5 ml) as needed and may be repeated every 2 to 3 minutes. In children the IV dose of glycopyrrolate is 0.002 mg (0.01 ml) per pound of body weight, not to exceed a dose of 0.01 mg (0.5 ml) in a single dose. As with the adult, this dose may be repeated every 2 to 3 minutes as needed.

Availability. Robinul (Robins): 0.2 mg/ml in 1 ml, 2 ml, 5 ml, and 20 ml ampules and vials. Each milliliter of glycopyrrolate contains:
  0.2 mg Glycopyrrolate
  Water for injection
  0.5 to 0.9% Benzyl alcohol as preservative
  pH adjusted to 2.0 to 3.0 with sodium hydroxide or hydrochloric acid

Summary

The anticholinergics will serve primarily as adjunctive drugs during IV sedation procedures on dental outpatients. The selection of drugs for use will be based on the indication for its use, for example:

Longer procedures (more than 2 to 3 hours)	Glycopyrrolate
Amnesia	Scopolamine
Sedation	Scopolamine
Decreased cardiovascular action	Glycopyrrolate
Short procedure, no amnesia, no sedation	Atropine

Anticholinergics may be administered in combination with any of the drugs being discussed in this section, with the notable exception of lorazepam (Ativan). The use of scopolamine is not recommended in conjunction with this agent because of the intense amnesic effect and the increased possibility of emergence delirium produced by this combination.

INNOVAR

Innovar is the trade name (Janssen Pharmaceutica) of a combination of two drugs—a long-acting, potent, nonphenothiazine tranquilizer of the buterophenone type (droperidol) and a potent, short-acting narcotic (fentanyl).

When administered intravenously this combination of drugs produces a state termed *neuroleptanesthesia* or *neuroleptanalgesia,* dependent on the dosage of drugs administered.

The term *neuroleptic* is a state of consciousness in which the patient has the following characteristics:
  Is sleepy, but not unconscious
  Is psychologically detached from the environment

Retains the ability to obey commands

Has diminished motor activity

The concept of neuroleptanesthesia, introduced in 1959, proposed combining the neuroleptic state with analgesia and amnesia to provide ideal circumstances for surgery.

The combination of droperidol and fentanyl provides neuroleptanalgesia, a state in which the patient retains consciousness yet is detached from the environment. The addition of N_2O and O_2 renders the patient unconscious in a state called *neuroleptanesthesia*.

Within the operating room neuroleptanesthesia is a very popular technique of general anesthesia, especially in the medically compromised patient (ASA III and IV). In the hospital environment in which the patient is nonambulatory the use of Innovar is rational; however, in the typical ambulatory outpatient dental situation or in short-stay surgery centers, the use of this drug combination makes less sense. The pharmacology of these agents will demonstrate this point.

Droperidol

Droperidol was synthesized in 1962 by Janssen Pharmaceutica in Belgium.

Pharmacology. Droperidol produces marked tranquilization and sedation. Other pharmacological actions of droperidol include the following:

1. Antiemetic actions
2. Potentiation of CNS–depressant drugs
3. Mild α-adrenergic blockade (and thus peripheral vasodilation) and a decrease in the pressor effects of epinephrine; droperidol can produce hypotension and a decrease in peripheral vascular resistance; however, this effect is not usually observed in therapeutic doses
4. The incidence of epinephrine–induced cardiac arrhythmias is reduced by the α-adrenergic properties of droperidol; however, there is no effect on the incidence of other types of arrhythmias

After IV administration the clinical actions of droperidol are observed in 3 to 10 minutes; however, the full effect may not be observed for as long as 30 minutes. This is a negative factor in the use of the drug for ambulatory, outpatient procedures, which are usually of short duration. Even more significant than its relatively slow onset of action is the fact that although the duration of clinical sedation and tranquilization produced by droperidol normally persists for 2 to 4 hours, al-

---

DROPERIDOL

The medical history of patients receiving droperidol should be checked for the following:

Possible hypovolemia (increases risk of hypotension with droperidol)

Allergy or hypersensitivity to droperidol

---

terations in the patient's state of consciousness may last up to 12 hours. This is the primary reason for not recommending this drug for use in outpatient procedures.

Indications. The following three indications are listed in the drug package insert for droperidol:

1. To provide tranquilization and reduce the incidence of nausea and vomiting in surgical procedures
2. For premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia
3. In neuroleptanalgesia, in which droperidol is administered concurrently with fentanyl to aid in tranquilization and decrease pain and anxiety

Warnings. Fluids and other countermeasures must be readily available to counteract hypotension if it should develop after administration of droperidol.

Droperidol potentiates the CNS–depressant properties of other drugs, including the narcotic analgesics, such as fentanyl. The initial dose of narcotics should be decreased to about one-fourth or one-third of the usually recommended dose.

Droperidol may be used safely in children over the age of 2 years; however, there are insufficient data to recommend its use in younger patients.

The safety of droperidol in pregnant patients has not been established with respect to its possible effect on the fetus. Droperidol, therefore, should be reserved for use in pregnant women and women of childbearing potential only when the benefits clearly outweigh the potential hazards of its use. In the elective, ambulatory, outpatient procedures practiced in dentistry, the use of droperidol is rarely indicated.

Precautions. The initial dose of droperidol should be reduced appropriately in the elderly,

debilitated, and other poor-risk patients. Other CNS–depressant drugs (narcotics, phenothiazines, barbiturates) have additive or potentiating effects when combined with droperidol. When a patient has received one of these prior to droperidol, the dose of droperidol should be reduced. In the same manner, the dose of the other CNS depressant is decreased if it is administered after droperidol.

Patients with significant liver or kidney disease should receive droperidol with caution because it is metabolized and excreted through these organs.

Adverse reactions. The most frequently reported adverse reactions to droperidol are hypotension and a mild tachycardia. Both of these effects usually resolve without drug management. The management of the hypotension, if severe or prolonged, is to administer IV fluids to the patient in an effort to increase fluid volume. Other adverse reactions include the following:

Postoperative drowsiness

Extrapyramidal symptoms, such as dystonia, akathisia, and oculogyric crisis; management occurs through use of diphenhydramine administered intravenously

Restlessness, hyperactivity, anxiety

Dizziness

Chills, shivering, or both

Laryngospasm, bronchospasm

Postoperative hallucinations

Respiratory depression, apnea, and muscular rigidity can develop when droperidol is administered with fentanyl. If permitted to remain untreated, these may lead to respiratory arrest.

The use of droperidol in the ambulatory outpatient is not recommended.

Droperidol is combined with the short—acting narcotic analgesic fentanyl to produce the combination called Innovar. Fentanyl has previously been discussed (see p. 340).

Effects of Innovar

The use of Innovar alone will usually not produce loss of consciousness. It will produce a state of neuroleptanalgesia, which was described at the beginning of this section.

When Innovar is used, both pharyngeal and laryngeal reflexes will be obtunded and care must be taken to protect the patient's airway. Fentanyl possesses mild emetic properties that are effectively counterbalanced by the potent antiemetic properties of droperidol.

One of the most significant concerns when In-

INNOVAR	
Proprietary name	Innovar
Classification	Neuroleptic
Availability	Droperidol, 2.5 mg/ml
	Fentanyl, 0.05 mg/ml
Average sedative dose	1-2 ml
Maximal single dose	0.5 1 ml
Maximal total dose	0.5-1 ml

NOTE: *Innovar is not recommended for use in outpatient procedures.*

novar is used is the potential for the production of respiratory depression. Innovar produces depression of the medullary respiratory center, raising the threshold to arterial CO_2 tension. Large doses of fentanyl may produce apnea.

The fentanyl component may also produce skeletal muscle rigidity of the thoracic and abdominal walls. Although not common, this action is related to the speed of injection of the drug and may be effectively prevented by the slow injection of Innovar or fentanyl. Should it develop, assisted or controlled ventilation is required, with the possible need for a neuromuscular blocking agent such as succinylcholine.

Contraindications. Contraindications to the administration of Innovar are allergy or hypersensitivity to either the droperidol or fentanyl component.

Warnings. The safety of fentanyl in patients who have taken MAO inhibitors within 14 days has not been established and is therefore not recommended. The safety of Innovar in patients under 2 years of age has not been established and is therefore not recommended.

Pregnant patients should not be administered Innovar unless the benefits of its administration clearly outweigh the potential hazards of its use. For this reason the use of Innovar cannot be recommended for the pregnant patient in the outpatient dental environment.

Adverse reactions. Adverse reactions to Innovar are the same as those for droperidol and fentanyl, which have been previously listed. The two major adverse reactions are hypotension and respiratory depression.

Orthostatic hypotension, primarily caused by

the droperidol, is another factor to consider in the ambulatory patient. Positional changes may produce dramatic decreases in the patient's blood pressure after droperidol administration. The fact that droperidol's duration of activity is approximately 8 hours requires the patient and his escort to be fully aware of this possibility.

Dosage. As with all intravenously administered drugs, the dose of Innovar should be individualized. Anesthesia is induced with a dose of 1 ml of Innovar per 20 to 25 pounds (1 ml per 9 to 11 kg). This dose must be administered slowly (over 5 to 6 minutes) to minimize the risk of muscular rigidity. Once the patient is heavily sedated with Innovar, N_2O-O_2 is added, unconsciousness occurs, and other general anesthetic drugs may be added. In the absence of N_2O-O_2, the patient remains conscious yet sedated.

Availability. Innovar (McNEILAB): 0.05 mg/ml fentanyl citrate (Sublimaze) and 2.5 mg/ml droperidol (Inapsine) in 2 ml and 5 ml ampules. Lactic acid is added to adjust the pH of the solution to 3.5 ± 0.3.

Summary

Innovar is a very popular combination of drugs for the production of neuroleptanalgesia or neuroleptanesthesia. As used in the hospitalized patient in whom postoperative recovery can be carefully monitored, neuroleptanesthesia and neuroleptanalgesia are excellent techniques. For outpatient procedures the use of Innovar is not recommended because the duration of action of one of its components—droperidol—is 8 hours, entirely too long for ambulatory patients. Innovar cannot, therefore, be recommended for use in the outpatient dental environment.

The combination of droperidol and fentanyl appears to be an illogical combination of drugs. Fentanyl, with its 45-minute duration of action, combined with droperidol's 8-hour duration of action, does not make sense. As used in the hospital, a patient will receive an initial dose of the Innovar combination. After this there is no longer a need to readminister droperidol for approximately 2 to 4 hours (usual duration of its sedative actions); however, the narcotic actions will disappear within 45 minutes. Therefore, individual doses of fentanyl are readministered as needed during the procedure. In surgical procedures of longer duration, an initial dose of Innovar or droperidol is administered and a longer-acting narcotic such as morphine is substituted for fentanyl.

A word of caution is needed before this section is concluded. Many doctors will employ nurse anesthetists to administer outpatient sedation or anesthesia in their dental offices. Many of these hospital-based persons will favor the use of Innovar in the dental patient. Remember that most of the procedures that these persons perform are on hospitalized patients in whom postoperative recovery will be closely monitored for many hours. Such is not the case in the typical dental situation. The use of Innovar should be discouraged in this situation. Other highly effective IV sedative medications are available for use in its place.

KETAMINE

Ketamine hydrochloride is a cyclohexane derivative closely related chemically and pharmacologically to phencyclidine, a veterinary anesthetic and prominent drug of abuse (known as "angel dust").

The type of anesthesia produced by ketamine has been termed *dissociative anesthesia.* It is a state in which the patient appears to be awake, has his eyes open, and is capable of muscular movement but appears to be unaware of, or dissociated from, the environment. Another term for the type of state induced by ketamine is *cataleptic anesthesia.* Profound analgesia and amnesia are associated with ketamine administration.

The cataleptic state produced by ketamine is an excitatory state, completely dissimilar from that seen after administration of the traditional general anesthetics such as halothane, thiopental, and meperidine. Blood pressure and heart rate, usually depressed somewhat during general anesthesia, are elevated after ketamine administration. Respiration is spontaneous and the airway is affected very little by the drug, the patient being capable of maintaining a patent airway throughout the procedure. Laryngeal and pharyngeal reflexes are intact or even hyperactive during ketamine anesthesia. When used in dental procedures it is important for an oropharyngeal pack to be placed to prevent contamination of the pharynx and/or larynx.

As used in the operating room, ketamine is used for short procedures, such as dilatation & curettage (D & C), surgical procedures on the skin, or dental procedures such as extraction or restorative procedures in pediatric patients. Another use of ketamine is in patients in whom multiple surgical procedures will be required, such as burn victims requiring multiple debridements and skin grafts.

KETAMINE

The medical history of patients receiving ketamine should be checked for the following:
Elevated blood pressure
Allergy or hypersensitivity to ketamine

KETAMINE

Proprietary names	Ketaject, Ketalar
Classification	Dissociative anesthetic
Availability	10, 50, 100 mg/ml
Average sedative dose	Not recommended
Maximal single dose	Not recommended
Maximal total dose	Not recommended

NOTE: *Administration of ketamine for outpatient sedation is not recommended.*

The onset of action of ketamine after IV administration is rapid (less than 1 minute), with a duration of clinical effect of approximately 10 minutes. The usual IV induction dose of ketamine is 1 to 4.5 mg/kg (approximately 0.5 to 2 mg/pound) administered over 1 minute. More rapid administration results in respiratory depression and an exaggerated pressor response. The duration of anesthesia may be prolonged with subsequent readministration of ketamine in doses of 0.5 mg/kg. The recovery period from ketamine anesthesia is prolonged the greater the dose of ketamine administered. An even more effective method of prolonging the anesthesia from ketamine is by administering local anesthesia for pain control and N_2O-O_2 for additional CNS depression. By administering these agents along with ketamine, the dose of ketamine is reduced, recovery is more rapid, and adverse recovery room phenomena minimized.

Recovery from ketamine-induced anesthesia is prolonged and is frequently associated with vivid dreams, hallucinations, and delirium. These emergence reactions are significantly more common in adults than in children. These reactions may last minutes or hours. Flashbacks—recurrence of these experiences—have occured months after the administration of ketamine. This is somewhat similar to flashbacks occurring after administration of LSD. Sussman (1974) reported that 24% of patients over 16 years of age reported emergence reactions, whereas only 8% of those under 16 years of age had the same response. Patients over the age of 65 years have decreased incidence of adverse emergence phenomena. The incidence of recovery phenomena may be minimized if the patient is permitted to remain undisturbed in a quiet, darkened, recovery area. IM administration of ketamine is associated with a decreased incidence of these reactions.

The use of ketamine is reserved for the younger patient as an induction agent (administered intramuscularly), after which an IV infusion can be started and the patient maintained with additional IV ketamine. It is also used as an anesthetic agent for diagnostic procedures, for minor operations of shorter duration, and for patients undergoing multiple procedures under general anesthesia.

Having had much experience with ketamine anesthesia with both inpatients and outpatients, I believe that the use of ketamine should be limited strictly to those doctors who have completed a residency in general anesthesia (because the patient is "asleep"), have gained experience in using ketamine (because it is so different from traditional general anesthetics), and have adequate recovery room facilities and monitoring available in the office.

ANTIDOTAL DRUGS

In concluding the section on pharmacology of IV sedation agents, several additional agents must be mentioned. These drugs will rarely be used; however, like an umbrella on a cloudy day, their presence is important. These agents may be called antidotal drugs, for their use will be reserved for reversing the adverse effects of drugs given previously. The following groups of drugs are discussed:
Narcotic antagonists
Agents for reversal of emergence delirium
Local anesthetic for extravascular or intraarterial drug administration
I believe that each of these categories should be represented in the emergency kit of all doctors administering drugs by the IM, submucosal, or IV route.

NARCOTIC ANTAGONISTS

The most significant side effect of the narcotic analgesics is their ability to produce respiratory depression. It is this more than anything else that limits the use of these potentially effective agents in dental practice. Less than adequate monitoring of respiratory efforts in the sedated patient has led to significant morbidity and death. The management of respiratory depression will be reviewed in Chapter 27. Administration of a narcotic antagonist is one of the basic steps in management of this situation. IV administration of a narcotic antagonist rapidly reverses the respiratory-depressant actions of the narcotic.

The first narcotic antagonist—nalorphine—became available in 1951, followed a year later by levallorphan. Both of these agents will reverse the analgesic effects of narcotics as well as their respiratory-depressant properties. Administered to a narcotic addict, these drugs can induce acute withdrawal syndrome. When administered in the absence of narcotic–induced respiratory depression, nalorphine and levallorphan can each produce respiratory depression and enhance the respiratory depression produced by barbiturates.

In the late 1960s naloxone became available and has replaced the former two agents as the drug of choice in reversing narcotic–induced respiratory depression. It is the only narcotic antagonist currently available that is free of narcotic agonist effects.

Recently nalbuphine, a narcotic agonist/antagonist analgesic, became available for use in anesthesia and sedation (see p. 344). Magruder (1982) used nalbuphine in place of naloxone for reversal of narcotic–induced respiratory depression, noting dramatic improvement within minutes, without any reversal of analgesia or euphoria. However, further research is necessary before nalbuphine can be recommended as the drug of choice for reversal of narcotic–induced respiratory depression.

Naloxone

Naloxone is a synthetic congener of the narcotic analgesic oxymorphone, from which it differs by the replacement of the methyl group on the N_2 atom by an allyl group.

Naloxone hydrochloride is soluble in water, dilute acids, and strong alkali. It is only slightly soluble in alcohol and practically insoluble in ether and chloroform.

Naloxone hydrochloride is an essentially pure

> ### *NALOXONE*
>
> The medical history of patients receiving naloxone should be checked for the following:
> Allergy or hypersensitivity to naloxone
> Narcotic dependence

---

narcotic antagonist. It does not possess any "agonistic" or opioid-type properties. Naloxone does not produce respiratory depression, as did levallorphan and nalorphine, nor does it produce psychotomimetic effects or miosis. When administered in the absence of narcotics, naloxone exhibits essentially no pharmacological activity.

Administered to a patient who is physically dependent on narcotics, naloxone will induce withdrawal symptoms. Naloxone in and of itself does not produce tolerance or lead to physical or psychological dependence.

After IV administration, improvement in respiration may be observed within 2 minutes. The duration of naloxone's effect is relatively short after IV use (about 30 minutes). The duration of respiratory depression produced by the narcotic will vary considerably with different narcotics. It is therefore possible for naloxone to successfully reverse the narcotic–induced respiratory depression, only to have that same effect recur after the duration of action of naloxone has passed. With meperidine and alphaprodine, the most commonly used narcotics in dentistry, this is unlikely to occur, although of these two, meperidine is the more likely to produce a recurrence of depression of breathing. After administration of naloxone the patient should not be discharged from the dental office for approximately 1 hour so that any recurrence of respiratory depression may be recognized and managed by readministration of naloxone if necessary.

Naloxone is indicated for use in narcotic depression, including respiratory depression, induced by any of the natural or synthetic narcotics, propoxyphene, and the narcotic agonist/antagonists pentazocine, nalbuphine, and butorphanol.

Contraindications. Naloxone is contraindicated for use in patients who are allergic or hypersensitive to it.

Warnings. Naloxone must be administered with extreme care to persons with known or suspected physical dependence on narcotics. The abrupt

NALOXONE	
Proprietary name	Narcan
Classification	Narcotic antagonist
Availability	0.02 and 0.4 mg/ml
Average therapeutic dose	0.4 mg (adult)
Maximal single dose	0.4 mg (adult)
Maximal total dose	1.2 mg (adult)*

*Lack of improvement after two or three doses usually indicates that respiratory depression is not produced by narcotics.

and complete reversal of narcotic effects may precipitate an acute abstinence syndrome (withdrawal). After naloxone reversal of narcotic–induced respiratory depression, the patient must be kept under surveillance in the event that repeated doses of naloxone might be needed. Respiratory depression produced by nonnarcotics (e.g., barbiturates) is not reversible by naloxone or other narcotic antagonists.

Precautions. In the event of narcotic–induced respiratory depression, naloxone is neither the most important nor the first step in patient management. Of greater importance is the patency of the airway and ventilation. All persons administering narcotic analgesics parenterally must be capable of maintaining the airway of the unconscious patient and of assisting or controlling the ventilation of the patient.

Adverse reactions. When administered to patients in the absence of narcotics, naloxone is essentially free of any side effects. In the presence of narcotics, abrupt reversal of narcotic depression may produce the following:

Nausea and vomiting
Sweating
Tachycardia
Increased blood pressure
Tremulousness

In the presence of pain, reversal of narcotic depression by large doses (greater than 0.4 mg) of naloxone may also significantly reverse analgesia, resulting in extreme discomfort and excitement. It has been reported in cardiac-risk patients that rapid reversal of narcotic–induced respiratory depression by large doses of naloxone has pro-

duced tachycardia and dramatic elevations in blood pressure resulting in left ventricular failure and pulmonary edema.

Dosage. Naloxone may be administered subcutaneously, intramuscularly, or intravenously. As mentioned previously, the onset of action after IV administration is within 2 minutes. After IM or subcutaneous administration, approximately 10 minutes might be required for onset of action. Duration of action is 30 minutes after IV administration and 1 to 4 hours after IM or subcutaneous administration. The potency of the drug will of course be greater after IV administration.

For the adult patient naloxone is diluted into a 0.1 mg/ml concentration. This is achieved by taking 1 mg of the 0.4 mg/ml concentration and adding 3 ml of diluent (e.g., 5% dextrose & water). Every 2 to 3 minutes 0.1 to 0.2 mg should be injected slowly intravenously while observing the patient for adequate reversal of respiratory depression—adequate ventilation and alertness without significant pain or discomfort.

Additional doses of naloxone may be required in some patients, depending on the type and dose of narcotic administered and the individual patient's response to naloxone. If repeated administration of naloxone is necessary, it is recommended that the IM route be given serious consideration since the duration of action of naloxone will be prolonged by this route of administration.

In children the initial dose of naloxone is 0.01 mg/kg of body weight administered intravenously, intramuscularly, or subcutaneously. This dose may be repeated every 2 to 3 minutes (IV) if the patient's response, or lack of it, requires it.

If for some reason naloxone must be administered subcutaneously or intramuscularly, the adult dose is 0.4 mg and the pediatric dose is 0.01 mg/kg. The onset of action will be slower; however, the duration of action will be significantly longer than occurs with IV administration.

Availability. Narcan (Endo): adults and children—0.04 mg/ml in 1 ml ampules and 10 ml vials; neonates—0.02 mg/ml in 2 ml ampules. Each milliliter of naloxone contains:

Either 0.02 or 0.4 mg/ml naloxone
8.6 mg Sodium chloride
2.0 mg Methylparaben and propylparaben in a ratio of 9:1 as preservatives
pH adjusted with hydrochloric acid

Nalbuphine

As mentioned in the introduction to narcotic antagonists, nalbuphine, a relatively new narcotic agonist/antagonist, has recently been used as an agent to reverse narcotic–induced respiratory depression. It appears to be as effective as naloxone but possesses the added benefit of not reversing analgesia when used in large doses. The dosage of nalbuphine used by Magruder was 0.1 mg/kg. Although a very promising addition to the armamentarium of narcotic antagonists, additional research is required before nalbuphine can be recommended over naloxone.

Summary

The availability of agents capable of reversing the significant unwanted effects of narcotics is quite important. However, it is significantly more important to remember that the occasion to use these drugs will *almost never develop if IV sedatives and narcotics are administered correctly*. The maximal doses of narcotics recommended in this and the following chapters will not produce respiratory depression in all but the most debilitated or acutely sensitive patients. However, maximal doses rarely need be administered. Adequate clinical effects will usually be achieved with doses below these maximal doses. The secret to success and safety with narcotics, as it is with all drugs, is to slowly titrate the agent to effect.

In 11 years of teaching IV sedation on the doctoral, postdoctoral, and continuing education levels, I have never had a patient who required a narcotic antagonist for reversal of narcotic–induced respiratory depression. Having the drug available is absolutely essential if narcotics of any type are administered by any route in the dental office. Routine narcotic reversal, as preached by some, is absolutely unnecessary and may in some cases prove dangerous (in cases in which postoperative pain is present the cardiovascular system may be overstressed).

AGENTS FOR REVERSAL OF EMERGENCE DELIRIUM

Several of the drugs previously discussed in this chapter have the disturbing propensity of producing what is now known as emergence delirium. During recovery from clinical actions of diazepam or scopolamine (the two agents most likely to produce this action), the patient appears to lose contact with reality. There may be increased muscular activity, and the patient may seem to be speaking but the sounds are unintelligible. A variety of responses may be noted; however, in all of them it is apparent that the patient is not returning to his "normal" state of consciousness. Until the mid-1970s management of this situation required monitoring of the patient and symptomatic treatment. Antidotal therapy was not available.

Physostigmine

Physostigmine is a reversible cholinesterase, similar in action to neostigmine, with the important difference that neostigmine, a quaternary compound, cannot cross the blood-brain barrier, whereas physostigmine, a tertiary ammonium compound, readily crosses the blood-brain barrier.

Actions. Physostigmine is extracted from the seeds of *Physostigma venenosum* (Calabar bean). It is a reversible anticholinesterase that increases the concentration of acetylcholine (ACh) at cholinergic transmission sites. The action of ACh is normally quite transient because of its rapid hydrolysis by the enzyme anticholinesterase. Physostigmine inhibits this action of anticholinesterase and thereby prolongs and intensifies the actions of ACh.

Being a tertiary ammonium compound, physostigmine crosses the blood-brain barrier to reverse the central toxic effects of anticholinergia and emergence delirium—anxiety, delirium, disorientation, hallucinations, hyperactivity, and seizures.

It has also been reported that physostigmine may reverse some of the CNS–depressant actions of diazepam; however, considerably more research must be carried out in this area. Should this be factual, oversedation with diazepam (an extremely rare occurrence) could be reversed by administering physostigmine.

Physostigmine is rapidly metabolized (60 to 120 minutes).

Contraindications. Physostigmine should not be administered to patients with asthma, diabetes, cardiovascular disease, or mechanical obstruction of the GI or genitourinary tracts.

Warnings. Physostigmine may produce excessive salivation, emesis, urination, and defecation. These are unlikely to develop if the drug is administered slowly intravenously at a rate of 1 mg/minute. More rapid administration can produce the preceding signs and symptoms as well as bra-

dycardia, hypersalivation, leading to respiration difficulties, and possibly convulsions.

Precautions. Atropine sulfate should always be available whenever physostigmine is administered since it is an antagonist and antidote for physostigmine.

Dosage. The usual adult dose of physostigmine for reversal of emergence delirium is 0.5 to 2 mg. The drug is administered *slowly* through the IV infusion at a rate of not more than 1 mg/minute. Maximal dose should not exceed 4 mg.

Availability. Antilirium (O'Neal, Jones & Feldman) 1.0 mg/ml in 2 ml ampules. Each milliliter of solution contains:

  1.0 mg Physostigmine salicylate
  0.1% Sodium bisulfite
  2.0% Benzyl alcohol
  Water for injection

Summary

Although emergence delirium is an extremely rare complication of sedative procedures, it can, and does, occur. Most often it is seen after the administration of scopolamine to a younger (less than 6-year-old) or older (more than 65-year-old)

patient. Management of emergence delirium is based primarily on symptomatic treatment. Physostigmine administration will hasten the reversal of signs and symptoms.

Agitation and excessive movement during or after sedation may also be a sign of hypoxia. The patency of the patient's airway and oxygenation of the lungs should always be considered prior to administration of a drug for what is presumed to be emergence delirium.

LOCAL ANESTHETIC FOR EXTRAVASCULAR OR INTRAARTERIAL DRUG ADMINISTRATION
Procaine

The last of the antidotal drugs—procaine—recommended for the emergency kit of the doctor administering parenteral medications is a local anesthetic with considerable vasodilating properties. The following are indications for use of this drug:

  Extravascular administration of an irritating chemical
  Intraarterial administration of a drug

In both cases the major problem is that of compromised circulation to either a localized area of tissue (extravascular injection) or a limb (intraarterial). Management requires restoration of blood flow.

A property of all injectable local anesthetics except cocaine is vasodilation. Of the drugs available

---

PHYSOSTIGMINE

The medical history of patients receiving physostigmine should be checked for the following:
  Asthma
  Diabetes mellitus
  Cardiovascular disease
  Mechanical obstruction of GI or genitourinary tract

PHYSOSTIGMINE

Proprietary name	Antilirium
Classification	Reversible anticholinesterase
Availability	1.0 mg/ml
Average therapeutic dose	0.5-2 mg
Maximal single dose	2 mg
Maximal total dose	4 mg

PROCAINE

The medical history of patients receiving procaine should be checked for the following:
  Allergy to ester-type local anesthetics
  Familial history of atypical plasma cholinesterase

PROCAINE

Proprietary name	Novocain
Classification	Local anesthetic
Availability	1% (10 mg/ml)
Average therapeutic dose	1-5 ml
Maximal single dose	1-5 ml
Maximal total dose	5 ml

today, procaine (Novocain) is the most vasodilating. This property makes procaine an ineffective drug for pain control (without the addition of a vasoconstrictor), but makes the drug eminently suitable for the reversal of blood vessel spasm.

The drug should be used in a 1% concentration without any vasoconstrictor added. More detailed discussion of management of these problems is found in Chapter 27.

Dosage. When required for management of extravascular injection, 1 to 5 ml of 1% procaine will be administered, as described in Chapter 27. For intraarterial administration, 1 to 2 ml of 1% procaine will usually be sufficient.

Availability. Novocain (Breon): 1% procaine in 2 ml and 6 ml ampules and 30 ml vials. Each milliliter of solution of 1% procaine contains:

10 mg Procaine

Less than 1 mg acetone sodium bisulfite as preservative

Less than 2.5 mg chlorobutanol (in vial only) as preservative

BIBLIOGRAPHY

Al-Khudhairi, D., Whitwam, J.G., and McCloy, R.F.: Midazolam and diazepam for gastroscopy, Anaesthesia **37**:1002, 1982.

Allen, G.D.: Dental anesthesia and analgesia, Baltimore, 1979, The Williams & Wilkins Co.

Allonen, H., Ziegler, G., and Klotz, U.: Midazolam kinetics, Clin. Pharmacol. Ther. **30**:653, 1981.

AMA Drug Evaluations, ed. 4: Drugs used for anxiety and insomnia, Chicago, 1980, American Medical Associaton.

AMA Drug Evaluations, ed. 4: General analgesics, Chicago, 1980, American Medical Association.

Andrews, P.R., and Mark, L.C.: Structural specificity of barbiturates and related drugs, Anesthesiology **57**:314, 1982.

Ausinch B., Malagodi, M.H., and Munson, E.S.: Diazepam in the prophylaxis of lignocaine seizures, Br. J. Anaesth. **48**:309, 1976.

Barclay, J.K.: Variations in amnesia with intravenous diazepam, Oral Surg. **53**:329, 1982.

Becsey, L., Malamed, S., Radnay, P., and Foldes, F.F.: Reduction of the psychotomimetic and circulatory side effects of ketamine by droperidol, Anesthesiology **37**:536, 1972.

Berggren, L., and Eriksson, I.: Midazolam for induction of anaesthesia in outpatients: a comparison with thiopentone, Acta Anaesthesiol. Scand. **25**:492, 1981.

Bidwai, A.V., Stanley, T.H., Roger, C., and Riet, E.K.: Reversal of diazepam induced postanesthetic somnolence with physostigmine, Anesthesiology **51**:256, 1979.

Brandsetter, R.D., and Gotz, V.P.: Recurrence of intravenous-diazepam induced phlebitis from oral diazepam, Drug Intell. Clin. Pharm. **17**:125, 1983.

Breimer, D.D.: Pharmacokinetics of methohexitone following intravenous infusion in humans, Br. J. Anaesth. **48**:643, 1976.

Brown, P.R.H., Main, D.M.G., and Wood, N.: Intravenous sedation in dentistry: a study of 55 cases using pentazocine and diazepam, Br. Dent. J. **139**:59, 1975.

Brown, C.R., Sarnquist, F.H., Canup, C.A., and Pedley, T.A.: Clinical, electroencephalographic, and pharmacokinetic studies of a water-soluble benzodiazepine, midazolam maleate, Anesthesiology **50**:467, 1979.

Burch, P.G., and Stansk, D.R.: The role of metabolism and protein binding in thiopental anesthesia, Anesthesiology **58**:146, 1983.

Caldwell, C.B., and Gross, J.B.: Physostigmine reversal of midazolam-induced sedation, Anesthesiology **57**:125, 1982.

Cascorbi, H.F.: Biotransformation of drugs used in anesthesia, Anesthesiology **39**:115, 1973.

Chambrias, P.G.: Evaluation of sedatives in dental practice: preliminary report, Aust. Dent. J. **15**:112, 1970.

Clark, E.O., Glanzer, N., and Turndorf, A.: The pattern of memory loss resulting from intravenously administered diazepam, Arch. Neurol. **36**:296, 1979.

Coleman, J., and Green, R.A.: Methohexital, a short-acting barbiturate, Anaesthesia **15**:411, 1960.

Conner, J.T., Katz, R.L., Pagano, R.R., and Graham, C.W.: RO 21-3981 for intravenous surgical premedication and induction of anesthesia, Anesth. Analg. **57**:1, 1978.

Corssen, G., Hayward, J.R., Gunter, J.W., and Groves, E.H.: A new parenteral anesthesia for oral surgery, J. Oral Surg. **27**:627, 1969.

Council on Dental Therapeutics, American Dental Association: List of accepted products, J. Am. Dent. Assoc. **105**:940, 1982.

Creedon, R.L.: Alphaprodine. In Wright, G.Z., editor: Behavior management in dentistry for children, Philadelphia, 1975, W.B. Saunders Co.

Dangers of Innovar: Med. Lett. Drugs Ther. **16**:42, 1974.

Davidau, A.: New methods in anaesthesiology and their use in dentistry: treatment of difficult patients and execution of complex procedures, Rev. Assoc. Med. Israelites France **16**:663, 1967.

Dixon, R.A., Atkinson, R.E., Kenyon, C., Lamb, D., Thornton, J.A., and Woodhead, S.: Subanaesthetic dosage of Althesin as a sedative for conservative dentistry: a controlled trial, Br. J. Anaesth. **48**:431, 1976.

Dixon, R.A., Bennett, N.R., Harrison, M.J., Kenyon, C., and Thornton, J.A.: I.V. flunitrazepam in conservative dentistry: a cross-over trial, Br. J. Anaesth. **52**:517, 1980.

Donaldson, D., and Gibson, G.: Systemic complications with diazepam, J. Oral Surg. **49**:126, 1980.

Dornauer, D., and Aston, R.: Update: midazolam maleate, a new water-soluble benzodiazepine, J. Am. Dent. Assoc. **106**:650, 1983.

Downes, J.J., Kemp, R.A., and Lambersten, C.J.: The magnitude and duration of respiratory depression due to fentanyl and meperidine in man, J. Pharmacol. Exp. Ther. **158**:416, 1967.

Driscoll, E.J., Zale, J.S., Lightbody, P.M., and Fiorucci, R.D.: Sedation with intravenous diazepam, J. Oral Surg. **30**:332, 1972.

Duncalf, D., Nagashima, H., and Duncalf, R.M.: Naloxone fails to antagonize thiopental anesthesia, Anesth. Analg. **57**:558, 1978.

Dundee, J.W., and Wilson, D.B.: Amnesic action of midazolam, Anaesthesia **35**:459, 1980.

Dundee, J.W.: New I.V. anaesthetics, Br. J. Anaesth. **51**:641, 1979.

Dundee, J.W., and Kawar, P.: Consistency of action of midazolam (letter), Anesth. Analg. **61:**544, 1982.

Dundee, J.W., Samuel, I.O., Toner, W., and Howard, P.J.: Midazolam: a water-soluble benzodiazepine: studies in volunteers, Anaesthesia **35:**454, 1980.

Dundee, J.W., Samuel, I.O., Wilson, D.B., Toner, W., and Howard, P.J.: Midazolam maleate: a water-soluble benzodiazepine: preliminary results, Br. J. Clin. Pharmacol. **9:**305P, 1980.

Everett, G.B., and Allen, G.D.: Simultaneous evaluation of cardiorespiratory and analgesic effects of intravenous analgesia using pentobarbital, meperidine, and scopolamine with local analgesia, J. Am. Dent. Assoc. **83:**155, 1971.

Facts and Comparisons: Butorphanol (package insert), St. Louis, September 1982, Facts and Comparisons, Inc.

Facts and Comparisons: Nalbuphine, St. Louis, September 1982, Facts and Comparisons, Inc.

Fassi, A., and Rosenberg, M.: Atropine, scopolamine and glycopyrrolate, Anesth. Prog. **26:**155, 1979.

Felpel, L.P.: Antianxiety drugs and centrally acting muscle relaxants. In Neidle, E.A., Kroeger, D.C., and Yagiela, J.A., editors: Pharmacology and therapeutics, St. Louis, 1980, The C.V. Mosby Co.

Felpel, L.P.: Sedative-hypnotics and central nervous stimulants. In Neidle, E.A., Kroeger, D.C., and Yagiela, J.A., editors: Pharmacology and therapeutics, St. Louis, 1980, The C.V. Mosby Co.

Foreman, P.A.: Flunitrazepam in outpatient dentistry, Anesth. Prog. **29:**50, 1982.

Forster, A., Gardaz, J.P., Suter, P.M., and Gemperle, M.: Respiratory depression by midazolam and diazepam, Anesthesiology **53:**494, 1980.

Forster, A., Juge, O., and Morel, D.: Effects of midazolam on cerebral blood flow in human volunteers, Anesthesiology **56:**453, 1982.

Forster, A., Morel, D., Bachman, M., and Gemperle, M.: Respiratory depressant effects of different doses of midazolam and lack of reversal with naloxone: a double-blind randomized study, Anesth. Analg. **62:**920, 1983.

Fragen, R.J., and Caldwell, N.J.: Recovery from midazolam used for short operations, Anesthesiology **53:**S11, 1980.

Fragen, R.J., Gahl, F., and Caldwell, N.J.: A water soluble benzodiazepine, RO 21-3981, for induction of anesthesia, Anesthesiology **49:**41, 1978.

Gal, T.J., DiFazio, C.A., and Moscicki, J.: Analgesic and respiratory depressant activity of nalbuphine: a comparison with morphine, Anesthesiology **57:**367, 1982.

Gebhart, G.F.: Narcotic analgesics and antagonists. In Neidle, E.A., Kroeger, D.C., and Yagiela, J.A., editors: Pharmacology and therapeutics, St. Louis, 1980, The C.V. Mosby Co.

Gelfman, S.S., Gracley, R.H., Driscoll, E.J., Wirdzek, P.R., Sweet, J.B., and Butler, D.P.: Conscious sedation with intravenous drugs: a study of amnesia, J. Oral Surg. **36:**191, 1978.

Gracely, R.H., Dubner, R., and McGrath, P.A.: Fentanyl reduces the intensity of painful tooth pulp sensations: controlling for detection of active drugs, Anesth. Analg. **61:**751, 1982.

Greenblatt, D.J.: Clinical pharmacokinetics of oxazepam and lorazepam, Clin. Pharmacokinet. **6:**89, 1981.

Greenblatt, D.J., Comer, W.H., Elliott, H.W., Shader, R.I., Knowles, J.A., and Ruelius, H.W.: Clinical pharmacokinetics of lorazepam III. Intravenous injection, J. Clin. Pharmacol. **17:**490, 1977.

Greenblatt, D.J., Sellers, E.M., and Shader, R.I.: Drug disposition in old age, N. Engl. J. Med. **306:**1081, 1982.

Greenblatt, D.J., and Shader, R.I.: Benzodiazepines, N. Engl. J. Med. **291:**1011, 1974.

Greenblatt, D.J., and Shader, R.I.: Benzodiazepines in clinical practice, New York, 1974, Raven Press.

Greenblatt, D.J., and Shader, R.I.: The clinical choice of sedative-hypnotics, Ann. Intern. Med. **77:**91, 1972.

Greenblatt, D.J., Shader, R.I., and Abernethy, D.R.: Current status of benzodiazepines, part 1, N. Engl. J. Med. **309:**354, 1983.

Greenblatt, D.J., Shader, R.I., and Abernethy, D.R.: Current status of benzodiazepines, part 2, N. Engl. J. Med. **309:**410, 1983.

Greenblatt, D.J., Shader, R.I., Franke, K., MacLaughlin, D.S., Harmatz, J.S., Allen, M.D., Werner, A., and Woo, E.: Pharmacokinetics and bioavailability of intravenous, intramuscular and oral lorazepam in humans, J. Pharm. Sci. **68:**57, 1979.

Greenfield, W.: Neuroleptanalgesia and dissociative drugs, Dent. Clin. North Am. **17:**263, 1973.

Gregg, J.M., Ryan, D.E., and Levin, K.H.: The amnesic actions of diazepam, J. Oral Surg. **32:**651, 1974.

Hare, S.A.: Anaesthetic induction and maintenance with flunitrazepam, S. Afr. Med. J. **52:**432, 1977.

Harvey, S.C.: Hypnotics and sedatives: the barbiturates. In Goodman, L.S., and Gilman, A., editors: Pharmacological basis of therapeutics, ed. 5, New York, 1975, Macmillan Publishing Co., Inc.

Harvey, S.C.: Hypnotics and sedatives: miscellaneous agents. In Goodman, L.S., and Gilman, A., editors: Pharmacological basis of therapeutics, ed. 5, New York, 1975, Macmillan Publishing Co., Inc.

Haslett, W.H.K., and Dundee, J.W.: Clinical studies of induction agents. XXIII: Reduction of respiratory complications by scopolamne and atropine, Anesth. Analg. **47:**174, 1968.

Heel, R.C., Brogden, R.N., Speight, T.M., and Avery, G.S.: Butorphanol: a review of its pharmacological properties and therapeutic efficacy, Drugs **16:**473, 1978.

Hegarty, J.E., and Dundee, J.W.: Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam, and flunitrazepam, Br. Med. J. **2**(6099):1384, 1977.

Hine, C.H., and Pasi, A.: Fatality after use of alphaprodine in analgesia for dental surgery: report of case, J. Am. Dent. Assoc. **84:**858, 1972.

Jensen, S., Huttel, M.S., and Schou Olesen, A.: Venous complications after IV administration of Diazemuls (diazepam) and Dormicum (midazolam), Br. J. Anaesth. **53:**1083, 1981.

Jusko, W.J., Gretch, M., and Gassett, R.: Precipitation of diazepam from intravenous preparations, JAMA **225:**176, 1973.

Kortilla, K., and Linnoila, M.: Recovery after intravenous sedation: a comparison of clinical and paper and pencil tests used in assessing late effects of diazepam, Anesthesia **31:**724, 1976.

Kortilla, K., and Linnoila, M.: Recovery and skills related to driving after intravenous sedation: dose-response relationship with diazepam, Br. J. Anaesth. **47:**457, 1975.

Kraynack, B.J., and Gintautas, J.G.: Naloxone: analeptic action unrelated to opiate receptor antagonism? Anesthesiology **56:**251, 1982.

Langdon, D.E., Harlan, J.R., and Bailey, R.L.: Thrombophlebitis with diazepam used intravenously, JAMA **223:**184, 1973.

Langrehr, D.: Pharmacodynamics and reversal of benzodiazepine-ketamine ataranalgesia, S. Afr. Med. J. **59:**425, 1981.

Larson, G.F., Hurlbert, B.J., and Wingard, D.W.: Physostigmine reversal of diazepam induced depression, Anesth. Analg. **56:**348, 1977.

Latto, I.P., and Lichtiger, M.: Intravenous and rectal anesthetic agents. In Lichtiger, M., and Moya, F., editors: Introduction to the practice of anesthesia, Hagerstown, 1974, Harper Row, Publishers.

Lebowitz, P., Cote, W., Daniels, A.L., Ramsey, F.M., Teplick, J.A.J, Davison, J.K.: Comparative cardiovascular effects of midazolam and thiopental in healthy patients, Anesth. Analg. **61:**771, 1983.

Levy, J.H., and Rockoff, M.A.: Anaphylaxis to meperidine, Anesth. Analg. **61:**301, 1982.

Litchfield, N.B.: Complications of intravenous diazepam: allergy? SAAD Digest **4:**228, 1981.

Litchfield, N.B.: Complications of intravenous diazepam: depression of respiration (an assessment of 16,000 cases), Anesth. Prog. **29:**11, 1981.

Lopez, J.: Physostigmine reversal of diazepam-induced respiratory arrest: report of case, J. Oral Surg. **39:**539, 1981.

Lundgren, S., and Rosenquist, J.B.: Amnesia, pain experience, and patient satisfaction after sedation with intravenous diazepam, J. Oral Surg. **49:**99, 1983.

Magruder, M.R., Delaney, R.D., and DiFazio, C.A.: Reversal of narcotic-induced respiratory depression with nalbuphine hydrpchloride, Anesth. Rev. **9**(4):34, 1982.

Main, D.M.G.: The use of diazepam in dental anaesthesia. In Knight, P.F., and Burgess, C.G., editors: Diazepam in anaesthesia, Bristol, 1968, John Wright & Sons, p. 85.

Maisel, G.M.: Midazolam: second generation benzodiazepine, Anesth. Prog. **28:**159, 1980.

McGimpsey, J.G., Kawai, P., Gamble, J.A.S., Browne, E.S., and Dundee, J.W.: Midazolam in dentistry, Br. Dent. J. **155:**47, 1983.

Miller, R.R.: Evaluation of nalbuphine hydrochloride, Am. J. Hosp. Pharm. **37:**942, 1980.

Minichetti, J., and Milles, M.: Hallucination and delirium reaction to intravenous diazepam administration: case report, Anesth. Prog. **29:**144, 1982.

Mitchell, P.F.: Diazepam-associated thrombophlebitis: a review and discussion of possible prevention, J. Am. Dent. Assoc. **101:**492, 1980.

Moore, P.A.: Narcotic agonists and antagonists for psychosedation, Fifth Annual Continuing Education Seminar in Practical Considerations in IV and IM Dental Sedation, Mt. Sinai Medical Center, Miami Beach, 1979.

Moore, P.A.: Valium: absorption, distribution, metabolism, and excretion, Fifth Annual Continuing Education Seminar in Practical Considerations in IV and IM Dental Sedation, Mt. Sinai Medical Center, Miami Beach, 1979.

Muller, W.E.: The benzodiazepine receptors, Pharmacology **22:**153, 1981.

Murray-Lyon, I.M., Young, J., Parkes, J.D., Knill-Jones, R.P., and Williams, R.: Clinical and electroencephalographic assessment of diazepam in liver disease, Brit. Med. J. **4:**265, 1971.

Nagashima, H., Karamanian, A., MaLovany, R., Rodnay, P., Ang, M., Koerner, S., and Foldes, F.F.: Respiratory and circulatory effects of intravenous butorphanol and morphine, Clin. Pharmacol. Ther. **19**(6):738, 1976.

Neidle, E.A.: Antimuscarinic drugs. In Neidle, E.A., Kroeger, D.C., and Yagiela, J.A., editors: Pharmacology and therapeutics, St. Louis, 1980, The C.V. Mosby Co.

Neidle, E.A.: Cholinergic drugs. In Neidle, E.A., Kroeger, D.C., and Yagiela, J.A., editors: Pharmacology and therapeutics, St. Louis, 1980, The C.V. Mosby Co.

O'Neill, R., and Verrill, P.: Intravenous diazepam in minor surgery, Br. J. Oral Surg. **7:**12, 1969.

Pakkanen, A., and Kanto, J.: Midazolam compared with thiopentone as an induction agent, Acta Anaesthesiol. Scand. **26:**143, 1982.

Pallasch, T.J., and Gill, C.J.: Butorphanol and nalbuphine: a pharmacologic comparison, Oral. Surg. 1985. (In press.)

Pallasch, T.J., and Gill C.J.: Naloxone-associated morbidity and mortality, Oral Surg. **52:**602, 1981.

Pandele, G., Chaux, F., Salvador, C., Farinotti, M., Duvaldestin, S.P.: Thiopental pharmacokinetics in patients with cirrhosis, Anesthesiology **59:**123, 1983.

Pandit, S.K., Dundee, J.W., and Keilty, S.R.: Amnesia studies with intravenous premedication, Anaesthesia **26:**421, 1971.

Pandit, V.A., Kothary, S.P., Samra, S.K., Domino, E.F., and Pandit, S.K.: Physostigmine fails to reverse clinical, psychomotor, or EEG effects of lorazepam, Anesth. Analg. **62:**679, 1983.

Price, H.L.: General anesthetics: intravenous anesthetics. In Goodman, L.S., and Gilman, A., editors: Pharmacological basis of therapeutics, ed. 5, New York ˜75 Macmillan Publishing Co.

Reves, J.G., Corssen, G., and Holcomb, C.: Comparison of two benzodiazepines for anaesthesia induction: midazolam and diazepam, Can. Anaesth. Soc. J. **25:**211, 1978.

Reves, J.G., Kissin, I., and Smith, L.R.: The effective dose of midazolam, Anesthesiology **55:**82, 1981.

Reves, J.G., Samuelson, P.N., and Lewis, S.: Midazolam maleate induction in patients with ischemic heart disease: haemodynamic observations, Can. Anaesth. Soc. J. **26:**402, 1979.

Richards, C.D.: On the mechanism of barbiturate anaesthesia, J. Physiol. (Lond.) **227:**749, 1972.

Richter, J.J.: Current theories about the mechanisms of benzodiazepines and neurolept drugs, Anesthesiology **54:**66, 1981.

Roesch, C., Haselby, K.A., Paradise, R.R., Krishna, G., Dierdorf, S., Wolfe, T.M., and Rao, C.C.: Comparison of cardiovascular effects of thiopental and pentobarbital at equivalent levels of CNS depression, Anesth. Analg. **62:**749, 1983.

Romagnoli, A., and Keats, A.S.: Ceiling effect for respiratory depression by nalbuphine, Clin. Pharmacol. Ther. **27:**478, 1980.

Rosenberg, H.: Physostigmine reversal of sedative drugs, JAMA **229:**1168, 1974.

Rosenberg, M.: Muscle rigidity with fentanyl: a case report, Anesth. Prog. **24:**50, 1977.

Safwat, A.M., and Daniel, D.: Grand mal seizure after fentanyl administration, Anesthesiology **59:**78, 1983.

Samuel, I.O., Clarke, R.S.J., and Dundee, J.W.: Some circulatory and respiratory effects of morphine in patients without preexisting cardiac disease, Br. J. Anaesth. **49:**927, 1977.

Samuelson, P.N., Reves, J.G., Kouchoukos, N.T., Smith, L.R., and Dole, K.M.: Hemodynamic responses to anesthetic induction with midazolam or diazepam in patients with ischemic heart disease, Anesth. Analg. **60:**802, 1981.

Scammon, F.L.: Fentanyl–O_2-N_2O rigidity and pulmonary compliance, Anesth. Analg. **62:**332, 1983.

Sethna, D.H., Moffitt, E.A., Gray, R.J., Bussel, J., Raymond, M., Conklin, C., Shell, W.E., and Matloff, J.M.: Cardiovascular effects of morphine in patients with coronary arterial disease, Anesth. Analg. **61:**109, 1982.

Simpson, P.: Lorazepam unsuitable for day surgery (letter), Br. Med. J. **6139**:703, 1978.

Smith, M.T., Eadie, M.J., and Brophy, T.U.: The pharmacokinetics of midazolam in man, Eur. J. Clin. Pharmacol. **19**:271, 1981.

Sokoll, M.D., Hoyt, J.L., and Gergis, S.D.: Studies in muscle rigidity, nitrous oxide, and narcotic analgesic agents, Anesth. Analg. **51**:16, 1972.

Southern, P., Rehder, K., and Didier, E.P.: Midazolam sedation and respiratory mechanics in man, Anesthesiology **55**:A367, 1981.

Steen, S.N., and Martinez, L.R.: Some pharmacologic effects of intravenous chlordiazepoxide, Clin. Pharmacol. Ther. **5**:44, 1964.

Sussman, D.R.: A comparative evaluation of ketamine anesthesia in children and adults, Anesthesiology **40**:459, 1974.

Taff, R.H.: Pulmonary edema following naloxone administration in a patient without heart disease, Anesthesiology **59**:576, 1983.

Tallman, J.F., Paul, S.M., Skolnick, P., and Gallager, D.W.: Receptors for the age of anxiety: pharmacology of the benzodiazepines, Science **207**:274, 1980.

Vandam, L.D.: Butorphanol, N. Engl. J. Med. **302**:381, 1980.

White, P.F.: Comparative evaluation of intravenous agents for rapid sequence induction: thiopental, ketamine, and midazolam, Anesthesiology **57**:279, 1982.

Winters, W.D., and Nakamura, J.: Agents used in general anesthesia and conscious sedation. In Neidle, E.A., Kroeger, D.C., and Yagiela, J.A., editors: Pharmacology and therapeutics, St. Louis, 1980, The C.V. Mosby Co.

Wood, M., and Wood, A.J.J.: Drugs and anesthesia: pharmacology for anesthesiologists, Baltimore, 1982, The Williams & Wilkins Co.

Yaksh, T.L., and Howe, J.R.: Opiate receptors and their definition by antagonists, Anesthesiology **56**:246, 1982.

Young, G.L.: Midazolam (Hypnovel), letter, SAAD Digest, **5**(6):156, 1983.