

Guidelines for selection of an agent

When selecting an agent for conscious sedation, the following factors should be taken into account:

- Degree of pain and discomfort caused by procedure
- Approximate duration of the procedure
- Degree of patient immobilization required to conduct procedure
- Patient's underlying medical condition (NPO status, renal/hepatic function, possible drug interactions, patient's allergies, neurologic status, age/development)
- Concurrent medications which have additive sedative effects
- Physician's familiarity and experience with specific agents and their routes of administration

For procedures, which involve pain, an opioid (morphine, fentanyl, meperidine) is usually a good choice. The combination of an opioid and a benzodiazepine is very effective in procedures where sedation/amnesia and pain control are required. However, this combination enhances the respiratory depression associated with these agents. It is recommended to begin with a lower dose of benzodiazepine (i.e. ½ dose) in these cases.

Benzodiazepines (midazolam, lorazepam, diazepam) are pure sedative and amnesic agents, with no effect on pain. They are appropriate selections for painless procedures. Chloral hydrate is another possible choice in procedures where pain is not an issue.

Pentobarbital can produce anesthesia as well as sedative/hypnotic effects when higher doses are used.

Important Notes:

- Intravenous sedative/analgesic drugs should be given in small incremental doses that are titrated to the desired endpoints of analgesia and sedation.
- Sufficient time must elapse between doses to allow the maximum effect of each dose to be assessed before further drug administration.
- When using non-intravenous routes (oral, rectal, intramuscular), allowance should be made for the time required for drug absorption before supplementation is considered.
- The concept of incremental drug administration improves patient comfort, decreases cost and decreases the potential risks associated with excessive dosing.
- The propensity for combinations of sedative and analgesic agents to potentiate respiratory depression emphasizes the need to appropriately reduce the dose of each component as well as the need to continually monitor respiratory function.

Reversal Agents:

Naloxone (Narcan®) (for opioids)

0.01-0.1mg/kg up to 2mg/dose IV, IM, ET, SC. (reverses analgesia and respiratory depression) Partial reversal can be accomplished with doses in the lower range. May repeat every 2-3 minutes PRN. Onset within 2 minutes, effect lasts 20-90 minutes. Give IVP undiluted over 30 seconds. When using the ET route dilute injection with 1-2ml of normal saline. The duration of action is shorter than most opioids, therefore extra doses may be needed every 1 to 2 hours. Please remember acute reversal of opioid induced analgesia may result in pain, hypertension, tachycardia. or withdrawal symptoms in patients with physical dependence to opiates.

Flumazenil (Romazicon®):

(for benzodiazepines)

0.01mg/kg IV (max 0.2mg), then 0.01mg/kg (max 0.2mg), given every minute up to a total dose of 1mg. Reverses sedation only. Onset within 1-3 minutes, peak effect in 6-10 minutes. Duration of action is usually less than 1 hour and is related to the dose given. The effect of flumazenil may wear off before benzodiazepines are eliminated, therefore extra doses may be necessary. Flumazenil may induce seizures in patients on chronic benzodiazepine therapy for seizure control or with tricyclic antidepressant overdoses.

Nitrous oxide

- Nitrous oxide (N₂O) is a general inhalation anesthetic. It is almost odorless, non-explosive gas with sedative, anesthetic, and analgesic activity.
- In combination with oxygen, nitrous oxide has a long and safe history of efficacy as an adjunct to surgical anesthesia, with minimal effects on organ function, including pulmonary function, when adequate ventilation is maintained. The drug also has good analgesic properties and is used as an analgesic in dentistry, labor, and acute pain of myocardial infarction. In dentistry, nitrous oxide-oxygen combinations are primarily indicated as sedation to minimize or eliminate apprehension and fear of dental procedures, along with some light analgesia; nitrous oxide sedation in dentistry is not indicated as a general anesthetic agent or substitute for IV sedation, local anesthetics, and narcotic analgesics.
- Nitrous oxide must be administered with at least 30% oxygen. Induction of anesthesia may be accomplished with 70% nitrous oxide and maintenance of anesthesia with concentrations between 30% and 70%. For sedation and analgesia, concentrations of 15% to 50% nitrous oxide with oxygen have been used. Nitrous oxide should NOT be administered without oxygen.
- Nitrous oxide is rapidly absorbed via inhalation. The gas is rapidly eliminated via the lungs, with minimal amounts eliminated through the skin.
- No patient should receive more than 24 hours of continuous inspired nitrous oxide.
- Nitrous oxide is contraindicated in patients with:
 - Hypovolemia, shock, or cardiac disease (severe hypotension).
 - Conditions such as air embolism, pneumothorax, pulmonary air cysts, or acute intestinal obstruction. Nitrous oxide should be used with caution for any major bowel surgery and avoided in any type of ileus. Nitrous oxide has been shown to cause gaseous distension of the bowel, which may lead to increased intraluminal pressures and the risk of rupture.
 - Patients with vitamin B12 deficiency (pernicious anemia), dihydropteridine reductase deficiency, and those with other nutritional deficiencies (alcoholics) are at increased risk of developing neurologic disease and bone marrow suppression with exposure to nitrous oxide.
 - Patients undergoing bleomycin therapy, due to the increased risk of developing pulmonary toxicity from the high oxygen concentrations used in the inhalation sedation technique.

- Patients with increased intracranial pressure. Nitrous oxide has been shown to cause significant increases in cerebral blood flow (CBF), which can adversely effect the brain. The increase in CBF can increase cerebral blood volume and intracranial pressure.
- Nitrous oxide does increase middle-ear pressure, therefore it is not recommended for middle-ear surgery or in patients with auditory problems.
- Oxygen should be briefly administered during emergence from prolonged anesthesia with nitrous oxide to prevent diffusion hypoxia.
- Nausea and vomiting occurs postoperatively in approximately 15% of patients.
- Inhalational anesthetics increase the neuromuscular blocking effect of nondepolarizing muscle relaxants (eg, pancuronium, tubocurarine, vecuronium) possibly through CNS effects or by altering prejunctional and postjunctional myoneural function.
- Chronic exposure to nitrous oxide may cause blood dyscrasias. Therefore, complete blood counts should be monitored in nitrous oxide abusers, health-care professionals chronically exposed incidentally, or patients receiving ongoing therapy with nitrous oxide.

Fentanyl

- Fentanyl is a potent short acting synthetic narcotic analgesic with pharmacologic effects similar to morphine and meperidine. It is an excellent agent for brief painful procedures.
- Fentanyl 0.1 mg is approximately equivalent in analgesic activity to morphine 10 mg or meperidine 75 mg.
- Pediatric dosing of 0.5-1mcg/kg/dose IV given every 3 to 5 minutes to achieve desired effect. Adults typically receive 25-50mcg doses titrated to desired outcome
- When fentanyl is used as an adjunct to other analgesic agents and/or sedatives, a lower total dose is prudent because the respiratory depressant effects are additive.
- If a patient has a glomerular filtration rate of 10 to 50 mL/minute, 75% of the normal fentanyl dose should be administered and 50% of the dose should be administered if the glomerular filtration rate is less than 10 mL/minute. An increase in sensitivity to the drug's effect is present in end-stage renal disease.
- No dosing adjustments are suggested for hepatic impairment.
- The intravenous injection should be administered undiluted over 3 to 5 minutes; rapid administration may result in respiratory paralysis or apnea.
- Respiratory depression due to fentanyl may persist beyond the period of analgesia
- The most common side effects with all opioids are CNS depression, respiratory depression, apnea, circulatory depression, hypotension, and shock. Muscle rigidity and chest wall spasms occur following rapid IV administration of fentanyl; bradycardia, arrhythmias, nausea, vomiting, constipation, seizures, facial puritus, and delirium have also occurred.
- Available data indicates that unlike morphine and meperidine, histamine release, which can cause hypotension, tachycardia, and erythema, occurs rarely with fentanyl, even with use of large doses
- Fentanyl is contraindicated in:

- Hypersensitivity to fentanyl or any component
- Fentanyl should be used with caution in:
 - Cardiovascular depression with nitrous oxide
 - Monoamine oxidase inhibitor therapy within 14 days
 - Hepatic or renal dysfunction
- Decreased respiratory reserve and compromised respiratory function
- Cardiac bradyarrhythmias
- Muscular rigidity
- Head injury or brain tumor
- Concomitant use of other CNS or respiratory depressants (eg, phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine, monoamine oxidase inhibitors, benzodiazepines) may increase adverse effects.
- Naloxone can be used to reverse respiratory and CNS depression due to fentanyl. Naloxone will also reverse analgesic effects.

Flumazenil

- Flumazenil is an effective antagonist of the central nervous system depressant effects of benzodiazepines.
- After conscious sedation or anesthesia, flumazenil should not be substituted for an adequate period of post-procedure monitoring. The availability of flumazenil does not reduce the risks associated with the use of large doses of benzodiazepines for sedation.
- Flumazenil has not been shown to be effective for the treatment of hypoventilation due to benzodiazepine administration.
- The half-life of flumazenil is shorter than that of the benzodiazepines, monitoring must be continued after patient awakens to guard against relapsing.
- For reversal of the sedative effects of benzodiazepines after conscious sedation, the usual dose of flumazenil in children 1 year or older is 0.01 milligram/kilogram (up to 0.2 mg) administered intravenously over 15 seconds. If adequate anesthesia reversal does not occur after an additional 45 seconds, further injections of 0.01 mg/kg may be repeated at 1-minute intervals, as needed up to 4 times. The maximum total dose is 0.05 mg/kg or 1 milligram, whichever is lower. In the event of re-sedation, repeat doses may be administered at 20-minute intervals as needed.
- Flumazenil should be administered as a series of small injections and not as a single bolus dose, so that reversal of sedation can be controlled to the appropriate endpoint and so that the potential for adverse effects can be minimized.
- Reversal of benzodiazepine-induced sedation occurs within 1 to 2 minutes after flumazenil administration. Peak effect is seen in 6 to 10 minutes. Duration of action is 20 minutes to 4 hours depending on the dose given.
- No dose adjustments are required in cases of renal failure.

- Flumazenil is rapidly eliminated from the body by hepatic metabolism. The clearance of flumazenil is decreased to 40 to 60% of normal in patients with moderate hepatic impairment; and to 25% of normal with severe impairment.
- Flumazenil is generally well-tolerated. Cardiac arrhythmias and bradycardia are reported rarely. Dizziness, increased sweating, headache, blurred vision, and injection site pain are the most common adverse effects. Seizures may occur with flumazenil use, especially in cases of cyclic antidepressant or mixed drug overdose.
- Flumazenil is contraindicated in:
 - Hypersensitivity to flumazenil, benzodiazepines, or any component
 - Patients who have been given a benzodiazepine for control of a potentially life-threatening condition (eg, status epilepticus or control of increased intracranial pressure)
 - Patients who exhibit signs and symptoms of serious cyclic antidepressant overdose.
- Flumazenil should be used with caution in:
 - Patients with a history of long-term benzodiazepine use (flumazenil may precipitate withdrawal symptoms, which may include seizures).
 - Flumazenil should be used with caution in the patients with head injuries (seizures or alterations in cerebral blood flow may occur).
 - If neuromuscular blocking agents are used, flumazenil should not be used until the effects of neuromuscular blockade have been fully reversed.
 - May induce panic attacks in patients with a history of panic disorder.
 - Liver disease
 - Drug and alcohol dependent patients

Ketamine

- Ketamine is a non-barbiturate anesthetic/analgesic/sedative agent structurally related to phencyclidine. Ketamine is the only single-agent anesthetic capable of producing a "dissociative" anesthesia (patient appears awake but in a trance-like state, disconnected with reality).
- Ketamine is useful as a sedative/analgesic in a variety of specialized procedures and clinical settings, particularly in children and patients with bronchospasm.
- For sedation and analgesia, intravenous doses of 0.25 to 2mg/kg (use smaller doses for sedation for minor procedures). Intravenous maintenance doses of 1/3 to 1/2 of the initial dose. Intramuscular doses of 2 to 5 mg/kg have been employed.
- Ketamine is metabolized in the liver and hepatic clearance is required for termination of clinical effects. A prolonged duration of action may occur in patients with liver impairment; dose reductions should be considered in these patients. Dose adjustments do not appear warranted in renal insufficiency.
- Respiratory depression with ketamine is infrequent and endotracheal intubation is not required in most patients. Impairment of respiration can become significant with high or rapid intravenous doses and in the presence of central nervous system injuries; respiratory depression or arrest more likely to occur in neonates.
- Adverse effects associated with ketamine include emergence phenomena (vivid dreams, hallucinations, delirium), cardiovascular stimulation (tachycardia, hypertension), hypersalivation, elevation of intracranial and intraocular

pressures, nausea, vomiting, skeletal muscle hyperactivity, nystagmus, laryngospasm, and skin rash; respiratory depression is not usually observed.

- Benzodiazepines (midazolam, lorazepam) are effective in preventing both cardiovascular stimulatory effects (eg, tachycardia, hypertension, increased pulmonary vascular resistance) and emergence phenomena (eg, unpleasant dreams, hallucinations, delirium) related to ketamine. It is important to note that concurrent use of benzodiazepines can prolong recovery time.
- The incidence of postoperative emergence reactions following ketamine anesthesia is lower in children than adults. The incidence is particularly low in children less than 10 years of age.
- Premedication with an anticholinergic agent (atropine, glycopyrrolate) will reduce ketamine-induced hypersalivation.
- The commercially available 100 milligram/milliliter concentration of ketamine is indicated for intramuscular use; it must be diluted for intravenous administration. The 10 milligram/milliliter preparation is intended for intravenous administration; it is not recommended for dilution.
- Intravenous ketamine should be given slowly (over at least 60 seconds); faster rates of administration can enhance pressor responses and respiratory depression.
- Ketamine is contraindicated in:
 - Conditions where a significant elevation of blood pressure is hazardous (eg, patients with poorly controlled hypertension, aneurysms, acute right- or left-sided heart failure, angina, cerebral trauma, recent myocardial infarction).
 - Known hypersensitivity to ketamine or any component
- Ketamine should be used cautiously in:
 - Patients with mild-to-moderate hypertension, chronic congestive heart failure, tachyarrhythmias, or myocardial ischemia
 - Neurotic traits or psychiatric illness (schizophrenia, acute psychosis)
 - Age less than 3 months.
 - Alcohol intoxication or a history of alcohol abuse
 - Acute intermittent porphyria
 - [HREF="/mdxcgi/display.exe?CTL=h:\mdxw32\hcs32\mdxcgi\MEGAT.SYS&SET=72956630&SYS=12&T=996&D=1&PRINTREADY=3&T1=958"Seizures](#)
 - [HREF="/mdxcgi/display.exe?CTL=h:\mdxw32\hcs32\mdxcgi\MEGAT.SYS&SET=72956630&SYS=12&T=915&D=1&PRINTREADY=3&T1=958"Glaucoma or elevated intraocular pressure](#)
 - Hyperthyroidism or patients receiving thyroid replacement
 - Pulmonary or upper respiratory infection (ketamine sensitizes the gag reflex, potentially causing laryngospasm)
 - Intracranial mass lesions, presence of head injury, globe injuries, or hydrocephalus

Meperidine

- Meperidine is a synthetic narcotic analgesic. Meperidine produces analgesia by interacting with opioid receptors in the CNS.
- The recommended dose is meperidine I V 0.5-1.5mg/kg given in incremental doses every 5 to 10 minutes to achieve desired effect; I M/PO 1-2mg/kg (max 100mg). Adults usually receive 25-50mg I V; 50-150mg I M/PO.
- When given orally, significant first-pass metabolism occurs, and less than 50% of the dose reaches systemic circulation.

- Meperidine should be infused by slow intravenous push (3 to 5 minutes). Patients should be monitored for respiratory depression.
- Meperidine is demethylated to form normeperidine, which is then hydrolyzed along with meperidine to normeperidinic acid and meperidinic acid. All of which are active metabolites. Hepatic impairment is reported to significantly impair meperidine elimination and as a result dosage reduction may be necessary.
- Normeperidine, a metabolite of meperidine and a toxic CNS agent, was found to be increased in patients with renal failure, and are associated with CNS excitatory effects which are often seen after multiple doses of meperidine.
- Patients with moderate renal failure (GFR 10 to 50 mL/min) should receive 75% of the normal dose at the usual intervals and patients with severe renal failure (GFR less than 10 mL/min) should receive 50% of the normal dose at the usual intervals.
- The primary side effects are hypotension, histamine release, and respiratory depression; other frequent adverse effects are nausea, vomiting, constipation, headache, confusion, biliary spasm, dry mouth, stomach cramps, urinary tract spasms, paradoxical CNS stimulation, increased ICP, skin rash, hives and palpitations. Pruritus is also common due to histamine release.
- Meperidine is contraindicated in:
 - Hypersensitivity to meperidine or any component
 - Monoamine oxidase inhibitors (within 2 weeks)
 - Intracranial lesions causing increased pressure
 - Atrioventricular flutter
 - Respiratory depression or coma
- Multiple doses in patients with renal failure and a predisposition to convulsions or seizures
- Meperidine should be used with caution in:
 - Hepatic impairment
 - Impaired respiratory function
 - Seizures
 - Tachycardias
- Concomitant use of other CNS or respiratory depressants (eg, phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine, monoamine oxidase inhibitors, benzodiazepines) may increase adverse effects.
- Naloxone can be used to reverse respiratory and CNS depression due to meperidine. Naloxone will also reverse analgesic effects.

Midazolam

- Midazolam is an imidazole benzodiazepine possessing the same sedative, hypnotic, anxiolytic, muscle relaxant, and anterograde amnesiac effects as other benzodiazepines. Midazolam is an appealing agent for sedation due to its rapid onset, short duration of action, anxiolytic, and amnesic effects.
- Midazolam has a shorter duration of action than lorazepam or diazepam.
- Midazolam has NO analgesic effect.
- Pediatric patients generally require higher dosages of midazolam than do adults. Patients less than 6 years may require higher dosages than older pediatric patients and may require closer monitoring
- For sedation/anxiolysis/amnesia prior to and during procedures for pediatric patients 6 months to 5 years, the recommended initial intravenous dose for use by intermittent injection is 0.05 to 0.1 mg/kg. A total dose of up to 0.6 mg/kg may be necessary to reach the desired endpoint but usually does not exceed a total of 6 mg.
- For sedation/anxiolysis/amnesia prior to and during procedures for pediatric patients 6 to 12 years, the recommended initial intravenous dose for use by intermittent injection is 0.025 to 0.05 mg/kg. A total dose of up to 0.4 mg/kg may be necessary to reach the desired endpoint but usually does not exceed a total of 10 mg.
- The manufacturer recommends dosing patients 12 to 16 years as adults for sedation/anxiolysis/amnesia prior to and during procedures. Some patients in this age range will require higher than recommended adult doses but the total dose usually does not exceed 10 mg.
- The dose of midazolam should be slowly titrated to achieve the desired effect. Some adult patients may respond to as little as 1 milligram. The 1 mg/mL formulation is recommended to facilitate slower injection. No more than 2 mg should be given intravenously over at least 2 minutes. An additional 2-minute period should be used to fully evaluate the sedative effect. Further titration should be done in small increments, waiting at least 2 minutes between increments to assess sedation. A total dose greater than 5 mg is not usually necessary.
- Maintenance doses in increments of 25% of the initial dose may be given to maintain the desired level of sedation, but only by slow titration. If narcotic premedication or other central nervous system depressants are used, patients will require approximately 30-50% less midazolam.
- The initial dose of midazolam should be administered over 2 to 5 minutes. Midazolam is water-soluble and takes approximately 3 times longer than diazepam to achieve peak electroencephalographic effects. Therefore an additional 2 to 3 minutes is needed to fully evaluate the sedative effect before initiating a procedure or repeating a dose. The amnesia (anterograde) produced by midazolam lasts approximately 1 hour.
- Midazolam should not be administered by rapid intravenous injection in the neonatal population. Severe hypotension and seizures have been reported following rapid intravenous administration, particularly with concomitant use of fentanyl.
- For sedation/anxiolysis/amnesia prior to for procedures, intramuscular (IM) midazolam can be used to sedate pediatric patients to facilitate less traumatic insertion of an intravenous catheter for titration of additional medication. The recommended dose of midazolam is 0.05 to 0.15 mg/kg IM. The total dose usually does not exceed 10 mg. If given with an opioid, the initial dose of each must be reduced.
- For sedation/anxiolysis/amnesia prior to diagnostic, therapeutic, or endoscopic procedures, a single oral dose of 0.25 to 0.5 mg/kg is recommended. The dose depends upon the patient status and desired effect. Younger patients (6 months to 5 years) and less cooperative patients may require the higher dose. Cooperative and older patients (6 to 15 years old) may require only 0.25 mg/kg. For patients with cardiac or respiratory compromise or any other surgical risk or if the patient has received concomitant narcotics or other CNS depressants, a dose of 0.25 mg/kg should be considered. Maximum oral dose is 20 mg.

- Initial doses of intranasal midazolam are usually 0.2 mg/kg and are usually increased to a maximum of 0.5 mg/kg. Major disadvantages have included burning discomfort in the nasal mucosa and a bitter taste.
- The drug is metabolized in the liver and excreted in the urine (0.3% unchanged). Studies demonstrate significantly reduced midazolam clearance and prolonged drug half-life in patients with liver impairment.
- For mild to moderate renal failure, no dose adjustments are required. For severe renal failure (creatinine clearance less than 10 milliliters/minute), the dose should be decreased by 50%.
- Cardiorespiratory toxicity is generally mild when midazolam is administered in conjunction with continuous monitoring. Other side effects include respiratory depression, apnea, paradoxical excitement, headache, ataxia, rhythmic myoclonic jerking in preterm neonates (~8%), nystagmus, vomiting, injection site pain and phlebitis. Midazolam has been associated with respiratory depression and respiratory arrest most often when combined with other CNS depressants.
- Midazolam is contraindicated in:
 - Hypersensitivity to midazolam, other benzodiazepines or any component
 - Hypersensitivity to cherries or formulation excipients (syrup only)
 - Narrow angle glaucoma
- Midazolam should be used with caution in:
 - Pulmonary disease (may produce prolonged respiratory depression)
 - Hepatic or renal dysfunction (dose adjustments)
 - Open angle glaucoma (use only if they are receiving appropriate glaucoma therapy)
 - Shock or coma
 - Acute alcohol intoxication with depression of vital signs
 - Severe fluid or electrolyte imbalances
 - Congestive heart failure (slower elimination)
- Concomitant use of other CNS or respiratory depressants (eg, phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine, monoamine oxidase inhibitors) may increase adverse effects.
- Cimetidine, ranitidine, erythromycin, clarithromycin, diltiazem, verapamil, fluconazole, ketoconazole, itraconazole may increase midazolam serum concentrations
- Concomitant administration of a protease inhibitor (eg, indinavir, nelfinavir, ritonavir, saquinavir) and midazolam is not recommended. The manufacturers suggest that combined use of these agents could produce a decrease in the metabolism of midazolam resulting in midazolam toxicity and potentially severe adverse events.
- Coadministration of quinupristin/dalfopristin and midazolam should be undertaken with caution. Patients should be monitored for signs of excessive central nervous system depression. Doses of midazolam may need to be reduced.
- Flumazenil has been shown to selectively block the binding of benzodiazepines to CNS receptors, resulting in reversal of benzodiazepine induced CNS depression, but not repository depression.

Morphine

- Morphine is a narcotic that produces analgesia by interacting with opioid receptors in the CNS, perhaps mimicking enkephalins and endorphins. The long duration of action makes morphine a poor choice for short procedures, but it works well for longer procedures like burn debridement and post-reduction fracture pain.

- The drug should be given by slow IV push over 3 to 5 minutes. Patients should be observed for hypotension and respiratory depression.
- Morphine primarily undergoes hepatic metabolism to inactive metabolites, which are renally excreted. It would be expected that dosage adjustment in renal failure would not be necessary. However, it has been recommended that patients with moderate renal failure (GFR 10 to 50 mL/min) receive 75% of the normal dose at the usual intervals, and patients with severe renal failure (GFR less than 10 mL/min) receive 50% of the normal dose at the usual intervals. These recommendations are based on actual reports of decreased morphine clearance in renal failure patients, and the possibility that morphine-6-glucuronide may have some narcotic activity.
- The duration of action of morphine is prolonged in patients with hepatic insufficiency.
- The most common side effects with all opioids are CNS depression, respiratory depression, apnea, circulatory depression, hypotension, and shock. Other adverse effects include hallucinations, sexual dysfunction, nausea, vomiting, constipation, urinary retention, renal failure, miosis, dyspnea, urticaria, rash, pruritus, headache, peripheral vasodilatation, increased ICP and histamine release.
- Infants less than 3 months of age are more susceptible to respiratory depression.
- Respiratory depression due to morphine may persist beyond the period of analgesia.
- Morphine is contraindicated in:
 - Hypersensitivity to morphine or any component
 - Respiratory depression or acute or severe bronchial asthma
 - Paralytic ileus
- Morphine should be used with caution in:
 - Head injury, other intracranial lesions, or increase in intracranial pressure
 - Acute asthma attack
 - Chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, and pre-existing respiratory depression, hypoxia or hypercapnia
 - Compromised blood pressure
 - Pregnancy
 - Atrial flutter and other supraventricular tachycardias
- Seizure disorders
- Severe hepatic impairment
- Severe renal impairment
- Hypothyroidism
- Addison's disease
- Prostatic hypertrophy or urethral structure
- Acute abdominal pain
- Biliary tract disease
- Concomitant use of other CNS or respiratory depressants (eg, phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine, monoamine oxidase inhibitors, benzodiazepines) may increase adverse effects.
- Naloxone can be used to reverse respiratory and CNS depression due to morphine. Naloxone will also reverse analgesic effects.
- When morphine is used as an adjunct to other analgesic agents and/or sedatives, a lower total dose is prudent because the respiratory depressant effects are additive.

Naloxone

- Naloxone is a pure narcotic antagonist. Naloxone is a synthetic N-allyl derivative of oxymorphone. It antagonizes respiratory depression, analgesia, psychotogenic, dysphoric, miotic, and other pharmacologic effects of narcotic analgesics.
- Naloxone is useful for narcotic-induced respiratory depression due to: natural and synthetic narcotic analgesics (morphine, codeine, fentanyl, meperidine, hydromorphone), diphenoxylate (in Lomotil®), propoxyphene, and pentazocine).
- The usual initial pediatric dose is 0.01 mg/kg administered intravenously, intramuscularly, subcutaneously, or via the endotracheal tube. If this dose does not result in the desired clinical improvement, a subsequent dose of 0.1 mg/kg (up to 2mg/dose) may be administered. This dose may be repeated at 2 to 3 minute intervals to the desired degree of reversal.
- For adults an initial dose of 0.4 to 2 milligrams intravenously is recommended. If the desired degree of counteraction and improvement in respiratory function is not obtained, the dose may be repeated at 2 to 3 minute intervals.
- For the partial reversal of narcotic depression following a painful procedure, smaller doses of naloxone are usually sufficient. Doses should be titrated to allow for adequate ventilation and alertness without significant pain or discomfort. Larger than necessary doses of naloxone may result in reversal of analgesia and increase in blood pressure. Too rapid reversal may induce nausea, vomiting, sweating or circulatory stress. Repeat doses may be required within 1 to 2 hour intervals.
- It is recommended that naloxone be given in undiluted by rapid intravenous push over less than 30 seconds.
- Intramuscular or subcutaneous administration may be required if the intravenous route is unavailable. The onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of naloxone. The intramuscular route produces a more prolonged effect than intravenous administration. The requirement for repeat doses of naloxone, will also be dependent upon the amount, type, and route of administration of the narcotic being antagonized.
- Onset of effect is 2 to 3 min and duration is 20 min to 90min. Rapid hepatic metabolism by conjugation with glucuronic acid is followed by 65% of an intravenous dose excreted renally as conjugated metabolites.
- No specific dosage adjustment of naloxone is necessary in renal failure
- Adverse effects include prolonged partial thromboplastin time, hypotension, hypertension, arrhythmias, pulmonary edema, ventricular fibrillation, hepatotoxicity, and opiate withdrawal symptoms.
- Naloxone is contraindicated in:
 - Hypersensitivity to naloxone or any component
- Naloxone should be used with caution in:
 - Dependence may precipitate withdrawal symptoms.
 - Concurrent cardiotoxic drugs.
 - Pre-existing cardiac disease.
 - Intramuscular or subcutaneous injections in patients who are hypotensive or have impaired peripheral circulation.

Chloral Hydrate

- Chloral hydrate is a short acting sedative-hypnotic agent.
- Chloral hydrate may be used preoperatively or pre-procedurally to allay anxiety or produce sedation. Chloral hydrate is often used in children because many clinicians believe it produces less paradoxical excitement than the barbiturates; however, no well-controlled studies have confirmed this.
- Chloral hydrate is considered by some to be the drug of choice for sedation of children before diagnostic and dental procedures. It is used for conscious sedation during computerized tomography, MRI scans, and for dental procedures at oral or rectal doses of 50 to 100 milligrams/kilogram.
- Children with neurologic disorders and children greater than 48 months of age have a much greater sedation failure rate than other children.
- Chloral hydrate is hepatically metabolized to trichloroethanol (active) and trichloroacetic acid (inactive). The active metabolite produces the majority of the hypnotic effects for the drug. The metabolites are excreted in the urine. Chloral hydrate should be avoided in patients with moderate to severe renal failure (glomerular filtration rate less than 50 mL/minute).
- Adverse effects include arrhythmias, paradoxical excitement, ataxia, headache, gastric irritation, nausea, vomiting, diarrhea, leukopenia, eosinophilia, alterations in sleep patterns, respiratory depression, respiratory arrest, and cutaneous reactions.
- Chloral hydrate is contraindicated in:
 - Hypersensitivity to chloral hydrate or any component
 - Severe or marked hepatic or renal impairment
- Chloral hydrate should be used with caution in:
 - History of gastritis, esophagitis, or gastric/duodenal ulcers
 - Mentally depressed patients or those with suicidal tendencies
 - Severe cardiac disease
- A carcinogenic potential is associated with accumulation of trichloroethylene, a metabolite of chloral hydrate. The risk is theoretical and evidence is insufficient to warrant selection of an alternative agent.

Pentobarbital

- Pentobarbital is a short acting barbiturate. It is primarily used preoperatively or pre-procedurally to relieve anxiety and provide sedation. It is an excellent choice for painless procedures (eg, CT/MRI). The drug has NO analgesic properties.
- Pentobarbital can produce all degrees of depression of the central nervous system, from sedation to general anesthesia depending on the doses used.
- Pentobarbital 2 to 6 milligrams/kilogram can be infused intravenously into pediatric patients for sedation. The drug should be infused slowly in increments of 25% to 50% of the total dose and titrated to patient response. The recommended pediatric dose of intramuscular pentobarbital is 2 to 6 milligrams/kilogram given as a single injection, not to exceed the typical adult dose of 150-200mg.

- A commonly used initial intravenous dose for an adult is 100 milligrams. If necessary, additional small increments may be administered up to a total of 200 to 500 milligrams for normal adults. Adult intramuscular doses of pentobarbital are 150 to 200 milligrams.
- No specific dosage adjustment appears necessary in renal failure.
- The half-life of pentobarbital may be prolonged in some patients with severe liver damage suggesting that dosage reduction may be necessary. The half-life of pentobarbital may be shortened in epileptic patients on long term phenobarbital therapy.
- Administration of pentobarbital in combination with other sedatives or with narcotics increases the chance of respiratory compromise.
- Rapid intravenous injection may cause respiratory depression, apnea and hypotension. Administer undiluted slow IV push over 3 to 5 minutes. Do not inject intra-arterially. Intra arterial injection may cause arteriospasm and gangrene.
- Adverse effects include: tachycardia, bradycardia, arrhythmias, hypotension, nausea, vomiting, nystagmus, rash, phototoxicity, thrombophlebitis at IV site, apnea, laryngospasm, paradoxical hyperactivity and agitation.
- Pentobarbital is contraindicated in:
 - Porphyria
 - Known hypersensitivity to barbiturates or any component
- Pentobarbital should be used with caution in:
 - Patients with history of drug dependence or abuse
 - Patients with impaired liver function
- Concomitant use of other CNS or respiratory depressants (eg, phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine, monoamine oxidase inhibitors, benzodiazepines) may increase adverse effects.

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Medication	Route	Dose	Maximum Doses	Onset	Peak effect	Duration	Notes	Reversal agent	Medication
		(mg/kg/dose)		(minutes)	(minutes)	(minutes)			
midazolam	IV	0.025-0.1	Usual adult dose IV 1-2mg, IM 5mg, PO 7.5-15mg	1-5	5-7	45-60	adminster IV over 2-5 minutes to avoid hypotension; allow 2-5 minutes between doses to decrease chance of oversedation; pediatric [ats generally require higher doses than do adults. Pts <6yrs may require higher doses than older pediatric pts; IN use only 5mg/ml preparation; reduce dose when used in combination with opioids	flumazenil	midazolam
	IM	0.05-0.15		10-20	15 to 30 children/ 30-60 adults	60-120			
	PO	0.2-0.75	Maximun total doses: IV/IM 10mg, PO 20mg, PR 7mg, IN 6mg	10-30	20-50	60-120			
	PR	0.25-0.5		10-30	10-30	60-90			
	IN	0.2-0.5		5-15	10-15	30-60			
fentanyl	IV	0.5-1 mcg/kg/dose given every 3-5 min to desired effect (usual effective cumulative dose <u>2</u>mcg/kg)	adults: 25-50mcg incremental doses; recommended pediatric max dose for conscious sedation 4mcg/kg	1-3	5-15	analgesia 30-60	adminster IV over 3minutes; may repeat dose every 3-5 min to adjust to desired effect; reduce dose when used in combination with benzodiazepines	naloxone	fentanyl
midazolam & fentanyl combination	IV	midazolam 0.1mg/kg (2.5mg MAX) over 60 sec, wait 3 min; fentanyl 1mcg/kg	may repeat fentanyl in 1mcg/kg increments every 2 to 3 minutes to effect (100mcg MAX); may repeat midazolam	see midazolam and fentanyl information	see midazolam and fentanyl information	see midazolam and fentanyl information	caution must be used when using benzodiazepines and opioids together, since the risks of hypoxia and apnea are significantly greater than when	naloxone for respiratory depression	midazolam & fentanyl combination

		over 1 to 2 min	0.05mg/kg (5mg MAX)				either is used alone; have oximeter and cardiac monitor in place; airway equipment and naloxone available		
chloral hydrate	PO	25-100mg/kg, may repeat 25-50mg/kg after 30 min	1Gm infants/2Gm children or 100mg/kg	10-30	30-60	90-240	maximum doses of 2.5Gm have been utilized in some centers	none	chloral hydrate
	PR	25-100	1Gm infants/2Gm children	15-30	60	90-240	residual sedative effects may last up to 24hours		
ketamine	IV	0.25-2mg/kg, may repeat 1/2 dose every 10 min PRN	-	0.5-1	1	dissociation 15-30; analgesia 30-40; amnesia 60-120	contraindications include conditions where a significant elevation of blood pressure is hazardous (eg, aneurysm, heart failure, angina, cerebral trauma); risk of unpleasant dreams or hallucinations(rare in those <15 years of age), may be blunted by benzodiazepines; hypersalivation can be minimized with concurrent atropine or glycopyrrolate; rate of infusion should not exceed 0.5mg/kg/min	none	ketamine
	IM	2-5mg/kg, may repeat after 15 min	-	3-15	5-30	dissociation 15-30; recovery 90-150			
morphine	PO	0.1-0.6	adults 10-60mg per dose	20-30	60	3-5hours	use prompt release morphine preparations when giving orally	naloxone	morphine
	IV	0.05-0.15	adults 2-4mg may repeat in 5 min intervals up to 15mg	within 5	30-60	2-5hours	reduce dose when used in combination with benzodiazepines		
meperidine	PO	1-2	pediatric max 100mg; adults usually receive 50-150mg	10-15	45-60	120-240	administer IV over at least 3-5 minutes	naloxone	meperidine

	IV	0.5-1.5	pediatric max 100mg; adults 25-50mg given in incremental doses to desired effect	5	5-7	120-180	reduce dose when used in combination with benzodiazepines		
	IM	1-2	pediatric max 100mg; adults usually receive 50-150mg	10-15	30-60	120-240	incremental IV doses should be given at 25-33% of initial dose every 5-10 minutes		
nitrous oxide	INHAL	mixture with minimum of 30% O ₂	-	<5	-	<5 after discontinuing	contraindicated in pts with increased ICP; may cause gaseous distention of the bowel with risk of rupture; increases middle ear pressure	none	nitrous oxide
Pento-barbital	IV	2-6mg/kg total dose given in increments of 1-2 mg/kg every 2-5 min to desired effect	peds: 6mg/kg or 150-200mg adults: 100mg initially followed by small doses up to a total of 200-500mg	within 1	-	30-60	commonly patients are given 2mg/kg initially with additional doses of 1-2mg/kg given every 5 minutes until adequate sedation is achieved	none	pentobarbital
	IM	2-6	typical adult dose: 150-200mg	10-15	-	60-120	rapid administration is associated with hypotension and apnea		
propofol	IV	1-2mg/kg load, followed by infusion of 25-100mcg/kg/min	-	30 seconds	-	3-10	does not contain preservative; rapid growth of micro-organisms can occur; discard IV tubing and unused portion after 12 hours	none	propofol