RSPT 2317
Sedative-Hypnotic Agents

Barbiturates

Mechanism Of Action And Indications For Use:

Barbiturates interfere with the relay of sensory impulses to the cerebral cortex by inhibiting the ascending impulse conduction in the reticular formation. They can induce all levels of CNS divergence from mild sedation to deep coma. All barbiturates also depress the medullary respiratory center, resulting in a diminished respiratory drive. The degree of respiratory depression and CNS depression is primarily dose related.

Barbiturates are classified as long-acting, intermediate-acting, short-acting or ultra short-acting according to their onset of action and duration of effect. They are indicated for use as treatment in insomnia, as preoperative agents to reduce fear or anxiety, as aids to facilitate anesthesia and as anticonvulsant agents.

Contraindications:

Barbiturate sensitivity, liver disease, impaired renal function, patients with severe respiratory distress, respiratory disease in which dyspnea, obstruction or cor pulmonale is present, acute or chronic pain.

Precautions:

1. Barbiturates are habit forming. With continued use, tolerance and psychological and physical dependence may occur
2. Use with caution in patients who have suicidal or drug histories or who are mentally depressed.
3. Use with caution in elderly patients, debilitated patients and children as increased adverse reactions may occur.
4. Rapid IV administration may cause respiratory depression, apnea, laryngospasm and severe hypotension.

Adverse Reactions:

CNS: Somnolence, agitation, confusion, ataxia, vertigo, CNS depression, lethargy, nervousness, anxiety, delirium
Pulmonary: Hypoventilation, respiratory depression, apnea, laryngospasm, bronchospasm
Cardiovascular: Bradycardia, hypotension, syncope
GI: Nausea, vomiting, constipation, diarrhea, epigastric pain
Other: Injection into or near peripheral nerves may produce permanent neurological deficit
Hypersensitivity: Skin rash, angioneurotic edema, serum sickness
Acute intoxification: Unsteady walk, slurred speech, confusion, irritability, insomnia

Overdosage:

1 g oral dose produces serious poisoning
2-10 g may cause death
CNS and respiratory depression may progress to Cheyne-Stokes respirations along with tachycardia, hypotension, decreased body temperature and coma. Shock syndrome may also occur, manifested by apnea, circulatory collapse, respiratory arrest and possible death. With extreme overdosage, a flat EEG may result, which is reversible if hypoxic damage has not occurred. Pneumonia, pulmonary edema, cardiac arrhythmias, CHF and renal failure are possible complications of barbiturate overdose.

Treatment consists of providing supportive care, maintaining an airway, intubating with assisted ventilation if necessary and monitoring of vital signs and fluid balance. Emesis may be induced if patient

has not lost consciousness, with care taken to prevent aspiration. If renal function is normal, forced diuresis may be induced. In severe barbiturate overdose, hemodialysis may be necessary.

Table 1 - Barbiturates

Long-acting	**Short-acting**
(Onset: 60 min; Duration: 10-12 hr)	*(Onset: 10-15 min; Duration: 3-4 hr)*
Phenobarbital (Luminal)	Secobarbital (Seconal)
Mephobarbital (Mebaral)	Pentobarbital (Nembutal)
Intermediate-acting	**Ultra short-acting**
(Onset: 45-60 min; Duration: 6-8 hr)	*(Onset: <1 min; Duration: .5 hr)*
Amobarbital (Amytal)	Thiopental sodium (Pentothal)
Aprobarbital (Alurate)	Thiamylal sodium (Surital)
Butabarbital (Butisol)	Methohexital sodium (Brevital)
Talbutal (Lotusate)	

Benzodiazepines

Mechanism Of Action And Indications For Use:

Benzodiazepines are more commonly the drugs of choice used for sedative or hypnotic effects due to their efficacy and safety as demonstrated by considerable clinical documentation and experience. They exert their effect on subcortical levels of the CNS - primarily on the limbic system (emotional and behavioral responses) and on the reticular formation. However, benzodiazepines do not relatively affect the cerebral cortex as do the barbiturates. Benzodiazepines also directly facilitate the actions of γ-aminobutyric acid (GABA). GABA is a major inhibitory neurotransmitter located at presynaptic and/or postsynaptic neurons at various levels in the brain. The results produced include antianxiety effects, muscle relaxation, sedative or hypnotic effects and anticonvulsant effects. The Benzodiazepines exert minimal effects on the medullary respiratory center, making them safer to use than the barbiturates.

Benzodiazepines are indicated for use for the management of anxiety disorders, as hypnotics, as anticonvulsants, as muscle relaxants, for the management of acute alcohol withdrawal and as sedation for ventilator patients.

Contraindications:

Hypersensitivity to benzodiazepines, psychoses, acute alcoholic intoxication, patients in shock or coma with depression of vital signs.

Precautions

1. Use with caution in patients with liver and/or renal disease as the dosage may need to be reduced.
2. Continued use may lead to dependence.
3. Because of the potentiation of adverse reactions, use with caution in the elderly, patients with limited pulmonary reserve, the very ill and children.
4. Avoid alcohol or other CNS depressants with use of these agents.

Adverse Reactions

CNS: Sedation, sleepiness, confusion, disorientation, vertigo, syncope, depression, apathy, lethargy, fatigue, nervousness, irritability, delirium, headache, slurred speech, stupor, coma
Pulmonary: Decreased V_T, decreased f, apnea
Cardiovascular: Bradycardia, tachycardia, cardiovascular collapse, hypertension, hypotension, palpitations, edema
GI: Nausea, vomiting, anorexia, dry mouth, constipation, diarrhea, gastritis, increased salivation
Psychiatric: Behavior problems, hysteria, psychosis, suicidal tendencies
Other: Hiccoughs, fever, diaphoresis, paresthesias, muscular disturbances

Overdosage:
Symptoms include ataxia, hypotonia, hypotension, and coma. IV administration of diazepam has resulted in hypotension and respiratory or cardiac arrest.

Treatment consists of inducing vomiting and monitoring respiration, pulse and BP. Maintain an open airway at all times. With normal kidney function, induce forced diuresis. In critical situations, hemodialysis may be necessary.

Table 2 - Benzodiazepines

Long-acting *(Onset: 3-60 min; Peak 1-4 hr)*	**Short-acting** *(Onset: 3-60 min; Duration: 1-6 hr)*
Chlordiazepoxide (Librium)	Lorazepam (Ativan)
Diazepam (Valium)	Midazolam HCl (Versed)
	Triazolan (Halcion)

Narcotic Analgesics

Mechanism of Action and Indications for Use:

Narcotic analgesics comprise the opium alkaloids and their related derivatives. Specific receptor sites located throughout the CNS have been identified as opioid binding sites. Five categories of opioid receptors exist, with three categories being major sites for narcotic analgesics. Of major concern to the practitioner are the mu (μ) receptors that enhance morphine-like analgesia, resulting in euphoria, respiratory depression and physical depression. Morphine is a direct and continuous respiratory depressant that primarily suppresses the medullary respiratory center's response to increases in PCO_2.

Narcotic analgesics are indicated for use to relieve moderate to severe pain (as with MI), as a preoperative med, as an adjunct during anesthesia, in patients with acute pulmonary edema due to left sided heart failure and for management and sedation of intubated patients. Some are also used for their antitussive and antidiarrheal effects.

Contraindications:

Hypersensitivity to narcotics, diarrhea caused by poisoning, premature infants and during labor and delivery of premature infants.

Precautions:

1. With repeated use, tolerance, psychological dependence and physical dependence may occur.

2. Use with extreme caution in patients with head injury and in patients with increased ICP. Along with the respiratory depressant effects, these agents have the ability to increase CSF pressure.
3. Use with extreme caution in patients with asthma and in patients with other pulmonary disease due to these agents' ability to severely diminish respiratory drive, increase R_{AW} and suppress the cough mechanism.
4. Use with caution in the elderly, in debilitated patients and in children.
5. Do not use concurrently with alcohol or other CNS depressants.

Adverse Reactions:

Major hazards: Respiratory depression, apnea, circulatory depression, respiratory arrest, shock, cardiac arrest
Most frequent: Lightheadedness, dizziness, sedation, nausea, vomiting, sweating
CNS: Euphoria, dysphoria, delirium, insomnia, agitation, anxiety, fear, hallucinations, disorientation, lethargy, coma, mood changes, headache, tremors, convulsions
Cardiovascular: Tachycardia, bradycardia, hypotension, hypertension, palpitations, arrhythmias, syncope, peripheral circulatory collapse, facial flushing
Pulmonary: Respiratory depression, apnea, respiratory arrest, bronchospasm
GI: Dry mouth anorexia, constipation

Overdosage:

Symptoms include apnea, circulatory collapse, convulsions, CP arrest and death. Complications of OD include hypotension, bradycardia, hypothermia, pulmonary edema, pneumonia and shock.

Treatment consists of maintaining an open airway with ET intubation and assisted ventilation, if necessary. Naloxone (Narcan) is the preferred drug to administer for reversal.

Table 3 - Narcotics (IM & IV)

Narcotic	**Onset** *(min)*	**Peak** *(hr)*	**Duration** *(hr)*
Natural alkaloids of opium			
Morphine	15-60	.5-1	3-7
Codeine	15-30	.5-1	4-6
Semisynthetic derivatives			
Hydromorphone (Dilaudid)	15-30	.5-1	4-5
Oxymorphone (Numorphan)	5-10	.5-1	3-6
Synthetic derivatives			
Fentanyl (Sublimaze)	7-8		1-2
Meperidine (Demerol)	10-45	.5-1	2-4
Methadone (Dolophine)	30-60	.5-1	4-6

Miscellaneous Respiratory Depressants:

Other drugs that may depress respiration if ingested in sufficiently high quantities (OD) include formulations containing paraldehyde (Paral), chloral hydrate (Noctec), glutethimide (Doriden), propiomazine (Largon), Acetylcarbromal (Paxarel), methyprylon (Noludar), ethchlorvynol (Placidyl) and ethinamate (Valmid). Many of these are sleep inducing preparations that are relatively safe if administered within the normal dosage range.

The antipsychotic drugs may also induce respiratory depression, cardiovascular collapse, coma, or cardiac arrest if administered in excessive quantities. These agents include the neuroleptics (e.g. Haldol, Thorazine, Compazene, Phenergan), the tricyclic antidepressants (e.g. Asendin, Surmontil, Sinequan) and the tetracyclic antidepressants (e.g. monoamine oxidase inhibitors, Ludiomil, Desyrel).