SEDATIVE–HYPNOTICS (Non-Benzodiazepines)

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HISTORY AND EPIDEMIOLOGY

Sedative–hypnotics are xenobiotics that limit excitability (sedation) and or induce drowsiness and sleep (hypnosis).

Anxiolytics are medications prescribed for their sedative–hypnotic properties.

Sedative–hypnotic overdoses were described in the medical literature in 1853.

HISTORY AND EPIDEMIOLOGY

Barbiturates were introduced in 1903 and quickly supplanted older xenobiotics.

Benzodiazepines quickly became the most commonly used sedatives in the United States in the early 1960s.

Chlordiazepoxide, the first commercially available BZD, was initially marketed in 1960.

Since then, more than 50 BZDs have been marketed.

PHARMACODYNAMICS AND TOXICODYNAMICS

All Sedative–Hypnotics induce (CNS) depression.

Most clinically effective sedative–hypnotics produce their physiologic effects by enhancing the function of GABA-mediated chloride channels.

PHARMACOKINETICS AND TOXICOKINETICS

Most orally administered Sedative–Hypnotics are rapidly absorbed via the GI tract.

Barbiturates and BZDs are primarily absorbed in the small intestine.

Clinical effects are determined by their relative ability to penetrate the blood–brain barrier.

Xenobiotics that are highly lipophilic penetrate most rapidly.

CLINICAL MANIFESTATIONS

Slurred Speech, Ataxia, and Incoordination

Stupor or Coma

In most instances, respiratory depression parallels CNS depression.

However, not all sedative–hypnotics cause significant hypoventilation.

CLINICAL MANIFESTATIONS

Although oral overdoses of BZDs alone produce sedation and hypnosis, they rarely produce life-threatening hypoventilation.

Typically, the patient appears comatose but with normal vital signs.

In contrast, large (IV) doses of BZDs occasionally lead to potentially life-threatening respiratory depression.

CLINICAL MANIFESTATIONS

Hypothermia is described with most of the Sedative–

Hypnotics but is more pronounced with Barbiturates.

Fixed drug eruptions(Bullous) can appear over pressure-point areas → “Barbiturate Blisters,” this phenomenon is not specific to barbiturates → CO, Methadone, Imipramine, BZDs, and several others, can lead to the same finding.

DIAGNOSTIC TESTING

Electrolytes, Liver Function Tests, Thyroid Function Tests, BUN, Cr, Glucose, VBG, and CSF analysis

Diagnostic imaging studies, such as Neuroimaging of the head, are warranted on a case-by-case basis.

Routine laboratory screening for “drugs of abuse” generally is not helpful in the management of undifferentiated comatose adult patients.

DIAGNOSTIC TESTING

Concentrations of most other sedative–hypnotics are not routinely performed in hospital laboratories.

Because of its radiopacity, large ingestions of Chloral Hydrate are evident on abdominal XRay.

MANAGEMENT

Death secondary to Sedative–Hypnotic overdose usually results from Cardiorespiratory collapse.

Careful attention should focus on monitoring and maintaining adequate Airway, Oxygenation, and Hemodynamic support.

Supplemental Oxygen, Respiratory support, and prevention of Aspiration are the cornerstones of treatment.

MANAGEMENT

Hemodynamic instability should be treated initially with Volume Expansion.

Patients with Meprobamate and Chloral Hydrate overdoses occasionally present with both Respiratory Depression and Cardiac toxicity.

Cardiotoxic effects of Chloral Hydrate → Lethal Ventricular Dysrhythmias → Active Halogenated Metabolite Trichloroethanol causing myocardial sensitization to Catecholamines.

MANAGEMENT

In the setting of cardiac dysrhythmias from chloral hydrate, use of β-adrenergic antagonists such as Propranolol is reported to cause resolution of the dysrhythmia.

We recommend administering IV β-adrenergic antagonists in patients with chloral hydrate–induced dysrhythmias resistant to standard therapy.

MANAGEMENT

The use of GI decontamination should be decided on a case-by-case basis.

The benefits of activated charcoal (AC) must be balanced with the risks of its Aspiration and subsequent potential for pulmonary toxicity.

Phenobarbital overdose is one particular scenario in which MDAC increases elimination by 50% to 80%.

MANAGEMENT

Although the efficacy of Orogastric Lavage is controversial, orogastric lavage is reasonable in overdoses with xenobiotics that slow GI motility, specifically phenobarbital and meprobamate.

Orogastric lavage in the setting of oral BZD overdoses alone is not recommended because the benefits of lavage are minimal compared with the significant risks of Aspiration.

MANAGEMENT

Flumazenil, a competitive BZD antagonist, rapidly reverses the sedative effects of BZDs as well as zolpidem and its congeners.

However, Flumazenil can precipitate life-threatening BZD withdrawal in BZD-dependent patients.

Flumazenil use is also associated with Seizures, especially in patients who have overdosed on TCA.

MANAGEMENT

The exact length of the observation period will vary based on the patient's Clinical Presentation, Age, and the Type and Amount of xenobiotic(s) ingested.

Patients with symptomatic overdoses of long-acting sedative–hypnotics, such as Meprobamate and Clonazepam, or drugs that have significant enterohepatic circulation may require 24 hours of observation in the intensive care unit.

MANAGEMENT

Patients with mixed overdoses of various Sedative–Hypnotics and CNS depressants also warrant closer observation for respiratory depression because of synergistic respiratory depressant effects.

Barbiturates

Oral barbiturates are preferentially absorbed in the Small Intestine and are eliminated by both Hepatic and Renal mechanisms.

Alkalinizing the urine with sodium bicarbonate to a urinary pH of 7.5 to 8.0 can increase the elimination of phenobarbital.

Barbiturates

This procedure is not effective for the short-acting barbiturates because they have higher pKa values, are more protein bound, and are primarily metabolized by the liver with very little unchanged drug excreted by the kidneys.

Urinary alkalinization is utilized to ↓ the serum half-life of phenobarbital.

Barbiturates

The EXTRIP Workgroup recommends dialysis for cases of severe long-acting barbiturate poisoning presenting with Prolonged Coma, Respiratory Depression requiring Mechanical Ventilation, Shock, Persistent toxicity or Persistently ↑ serum concentrations despite MDAC.

Intermittent Hemodialysis and continuation of MDAC during dialysis is recommended.

Barbiturates

Early Deaths : Respiratory Arrest and Cardiovascular collapse.

Delayed Deaths : Acute Kidney Failure, Pneumonia, ARDS, Cerebral Edema, and Multiorgan System Failure as a result of prolonged Cardiorespiratory Depression.

Chloral Hydrate

First introduced in 1832, chloral hydrate belongs to one of the oldest classes of pharmaceutical hypnotics.

Although still used sporadically in children, its use has substantially decreased.

Chloral hydrate is well absorbed but is irritating to the GI tract.

Chloral Hydrate

It has extensive tissue distribution, rapid onset of action, and rapid hepatic metabolism by Alcohol and Aldehyde dehydrogenases.

Trichloroethanol is a lipid-soluble, active metabolite that is responsible for the hypnotic effects of chloral hydrate.

Chloral Hydrate

It has a serum half-life of 4 to 12 hours.

Cardiac Dysrhythmias are the major cause of death.

Chloral hydrate and its metabolites reduce myocardial contractility, and increase myocardial sensitivity to catecholamines.

Chloral Hydrate

Persistent cardiac dysrhythmias (ventricular fibrillation, ventricular tachycardia, torsade de pointes) are common terminal events.

β-Adrenergic Antagonists such as propranolol mitigate this myocardial sensitivity and are recommended in patients with chloral hydrate–induced dysrhythmias resistant to standard therapy.

Chloral Hydrate

In addition to Cardiotoxicity, Chloral Hydrate toxicity causes Vomiting, Hemorrhagic Gastritis, and rarely Gastric and Intestinal Necrosis, leading to Perforation and Esophagitis with Stricture formation.

Although large ingestions of chloral hydrate are evident on abdominal Radiographs because of its radiopacity, a normal radiograph should not be used to exclude chloral hydrate ingestion.

Bromides

Bromides were used in the past as “Nerve Tonics,” Headache Remedies, and Anticonvulsants.

Bromides tend to have long half-lives, and toxicity typically occurs overtime as concentrations accumulate in tissue.

Bromides

CNS function is progressively impaired → inappropriateness of behavior, headache, apathy, irritability, confusion, muscle weakness, anorexia, weight loss, thickened speech, psychotic behavior, ataxia, and eventually, coma.

Delusions and hallucinations occur.

Bromides lead to Hypertension, ↑ ICP, and Papilledema.

Carisoprodol and Meprobamate

Meprobamate was introduced in 1950 and was used for its muscle-relaxant and anxiolytic characteristics.

Carisoprodol, which was introduced in 1955, is metabolized to meprobamate.

Both drugs have pharmacologic effects on the GABA receptor similar to those of the barbiturates.

Carisoprodol and Meprobamate

Meprobamate causes profound hypotension from direct myocardial depression.

Adherent masses or bezoars of pills are reported in the stomach at autopsy after large meprobamate ingestions.

Orogastric lavage with a large-bore tube and MDAC is reasonable for patients with a significant meprobamate ingestion while keeping in mind the risk of aspiration.

Carisoprodol and Meprobamate

Whole-bowel irrigation is also reasonable if multiple pills or small concretions are suspected.

Patients can experience recurrent toxic manifestations as a result of concretion formation with delayed drug release and absorption.

Zolpidem, Zaleplon, Zopiclone, and Eszopiclone

These oral hypnotics have supplanted BZDs as the most commonly prescribed sleep aid medications.

Although they are structurally unrelated to the BZDs, they bind preferentially to the BZD site in the brain.

They have a lower affinity for BZD other sites → They have potent hypnotic effects with less potential for Dependence and Antiepileptics properties.

Zolpidem

Each of these xenobiotics has a relatively short half-life (6 hours or less), with zaleplon exhibiting the shortest half-life (1 hour).

Zolpidem

They are hepatically metabolized by various CYP450 enzymes.

In isolated overdoses, Drowsiness and CNS depression are common.

However, prolonged coma with respiratory depression is exceptionally rare.

Zolpidem

Isolated overdoses usually manifest with depressed level of consciousness without respiratory depression.

Zopiclone overdoses are rarely associated with Methemoglobinemia.

Tolerance to zolpidem and its congeners occurs, and as expected, withdrawal follows abrupt discontinuation of chronic use.

Zolpidem

The withdrawal syndrome is typically mild.

Flumazenil reverses the hypnotic and cognitive effects of these xenobiotics.

Deaths result when zolpidem is taken in large amounts with other CNS depressants.

Propofol

Propofol is a rapidly acting IV sedative–hypnotic that is both a postsynaptic GABAA agonist and induces presynaptic release of GABA.

In addition, propofol interacts with dopamine, promotes nigral dopamine release possibly via GABAB receptors, and has partial agonist properties at dopamine (D2) receptors.

Propofol

Propofol is used for procedural sedation and either induction or maintenance of general anesthesia, as well as an antiepileptic to manage status epilepticus.

It is highly lipid soluble, so it crosses the blood–brain barrier rapidly.

The onset of anesthesia usually occurs in less than 1 minute.

Propofol

The duration of action after short-term dosing is usually less than 8 minutes because of its rapid redistribution from the CNS.

Propofol use is associated with various adverse events→

Acutely, propofol causes dose-related respiratory depression.

Propofol

Propofol ↓ systemic Arterial pressure and causes Myocardial depression.

Although short-term use of propofol does not typically cause Dysrhythmias or Myocardial Ischemia, atropine-sensitive bradydysrhythmias are noted, specifically sinus bradycardia and Mobitz type 1 AV block.

Propofol

Short-term use of propofol in the perioperative setting is associated with a Myoclonic syndrome manifesting as Opisthotonus, Myoclonus, and sometimes Myoclonic Seizure–like activity.

Prolonged propofol infusions, typically more than 48 hours at rates of 4 to 5 mg/kg/h or greater, are associated with a life-threatening Propofol-Infusion Syndrome → Metabolic Acidosis, Cardiac Dysrhythmias, and Skeletal Muscle injury

Propofol

The clinical signs of propofol infusion syndrome often begin with the development of a new RBBB and ST-segment convex Elevations in the ECG precordial leads.

Predisposing factors to the development include young age, severe brain injury, respiratory compromise, concurrent exogenous administration of Catecholamines or Glucocorticoids, inadequate Carbohydrate intake, and undiagnosed Mitochondrial Myopathy.

Propofol

The unique nature of the carrier base of propofol, a milky soybean emulsion formulation, is associated with multiple adverse drug events such as impairment of macrophage function, hypertriglyceridemia, histamine-mediated anaphylactoid reactions, and impairment of platelet and coagulation function.

Additionally, the carrier base is a fertile medium for many organisms, such as enterococcal, pseudomonal, staphylococcal, streptococcal, and candidal species.

Etomidate

Etomidate is an IV nonbarbiturate, hypnotic primarily used for an anesthesia induction.

It is active at the GABA receptor.

Only the IV formulation is available.

The onset of action is less than 1 minute, and its duration of action is less than 5 minutes.

Etomidate

Etomidate is commercially available as a 2-mg/mL solution in a 35% propylene glycol solution.

Propylene glycol toxicity from prolonged etomidate infusions is implicated in the development of hyperosmolar metabolic acidosis.

Etomidate has both proconvulsant and antiepileptic properties.

Etomidate

Involuntary muscle movements are common during induction and are caused by etomidate interaction with glycine receptors at the spinal cord level.

Etomidate depresses adrenal production of cortisol and aldosterone; therefore, it is associated with adrenocortical suppression, usually after prolonged infusions.

Etomidate

Etomidate is associated with increased morbidity and mortality in critically ill and trauma patients.

However, the clinical significance of adrenal suppression from etomidate administration is disputed.

Dexmedetomidine

Dexmedetomidine is a central α2-adrenergic agonist that ↓ central presynaptic catecholamine release, primarily in the locus ceruleus.

Dexmedetomidine

It is used for procedural sedation in certain settings such as interventional radiology procedures and awake fiberoptic intubations.

Dexmedetomidine has minimal effect at the GABA receptor.

Unlike other sedative–hypnotics, it is not associated with significant respiratory depression.

Dexmedetomidine

Although mechanistically similar to Clonidine, dexmedetomidine does not appear to cause as much respiratory depression as clonidine.

Dexmedetomidine also has Analgesic effects.

Dexmedetomidine

Dexmedetomidine is currently only approved for use for less than 24 hours.

Extensive safety trials have not yet explored its use beyond 24 hours.

Dexmedetomidine

The most common adverse effects from its use are nausea, dry mouth, bradycardia, and varying effects on blood pressure (usually hypertension followed by hypotension).

Slowing of the continuous infusion may help to prevent or lessen the hypotensive effects.

Melatonin

Melatonin is naturally synthesized from tryptophan.

Ramelteon is a synthetic melatonin-analog that is FDA approved for the treatment of chronic insomnia.

Adverse effects of ramelteon are mild and usually include drowsiness, dizziness, fatigue, and headache.

Melatonin

In addition, ramelteon appears to have a low abuse potential and does not appear to be associated with a withdrawal syndrome or rebound insomnia.

Sedative/Hypnotics

GHB (gamma-hydroxybutyrate) → drowsiness, nausea/ vomiting, headache, loss of consciousness, loss of reflexes, seizures, coma, death

Methaqualone → euphoria/depression, poor reflexes, slurred speech, coma